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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

SEPTEMBER, 1935

ORIGINAL ARTICLES.

THE DIAGNOSIS OF PERIARTERITIS NODOSA.

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Although Rokitansky[1] is properly credited with the first pathologic description of periarteritis nodosa, he apparently had no appreciation of the clinical implications of his observations at necropsy. In 1866 Kussmaul and Maier[2] first correlated the clinical and the pathologic findings in this condition and gave it the generally accepted designation, periarteritis nodosa. Since that time over 200 cases have been reported in the literature, but the intravitam diagnosis is still unusual. From the accumulated knowledge of the pathologic sequences of this affection and its resultant clinical pictures it has seemed that a more orderly approach to the problem should render its recognition in life more ready.

The primary lesions are in the small arteries and arterioles, the larger elastic arteries and veins escaping. The general pattern is of an acute inflammation of the vessel wall, loss of muscle, repair and proliferation. Probably the inflammatory agent enters from the adventitial side of the vessel wall, being transmitted by the periarterial lymphatics.[3] There ensue degeneration of the muscle fibers of the media and coagulative and hyalin necrosis which may spread to the intima. A fibrinous and acute cellular exudate soon invades all layers of the arterial wall. This process is followed by a dense infiltration with lymphocytes, plasma cells and eosinophils. Injury of the intima leads to thrombosis. Medial injury and dila-

tation result in the formation of aneurysms. Frequently these aneurysms rupture and may thereby induce fatal hemorrhage. The acute exudative stage is succeeded by a fibroblastic proliferation in all coats with marked intimal thickening and a reduction of the lumen, replacement of the medial muscle and perivascular scarring. Canalization of thrombi may take place; and the organization of thrombosed aneurysms gives rise to firm periarterial nodules. During this reparative proliferation there remains a somewhat thinned infiltration of lymphocytes, plasma cells and eosinophils. In many of the reported cases there have been no gross periarterial nodules, and the pathologic diagnoses have not been reached until the microscopic examination. In these cases the arterial walls appear to have been strengthened promptly by reparative processes thus preventing aneurysm formation.

Many patients die in the acute phase of the disease, and in these cases the earlier lesions described would predominate. Other cases survive for a longer period, and in them the reparative processes are the most marked. The arterial lesions are not usually general, but affect widespread groups of vessels. These lesions cause infarction, degeneration, atrophy and scarring in the areas supplied. Gangrene is common if the hollow viscera are affected. The symptoms, signs and progress of cases probably depend as much upon the secondary reduction of blood supply to the various organs as they do on the primary arterial affection.

In 1928, Strong,[4] from his review of the literature, gave the following order of frequency of involvement of the arteries: 1, Renal; 2, coronary; 3, mesenteric; 4, hepatic; 5, arteries to other viscera; 6, cranial; 7, peripheral. The kidneys are commonly contracted and show much vascular scarring and infarction. When the coronary vessels are affected, the myocardium may show considerable patchy fibrosis. Gangrenous enteritis occurs secondary to mesenteric artery involvement. Probably peripheral artery lesions should rank higher in the above list, but specimens are not usually taken in routine autopsies. The organs least commonly involved are the brain and lungs.

From this brief discussion of the pathology of periarteritis nodosa, it may be inferred that the clinical manifestations of the disease may be extremely diversified. Indeed, it has been mistaken for "trichinosis, Werlhof's disease, typhoid fever, miliary tuberculosis, polymyositis, arteriosclerosis with sclerosis of the kidneys, neuritis multiplex, gastro-enteritis, pyemia, hemorrhagic nephritis, serositis tuberculosa, influenza with renal hemorrhage, purpura hemorrhagica," according to von Haun.[5] Harbitz[6] differentiated the gastro-intestinal, renal, neuromuscular, cardiac, cerebral and cutaneous forms of periarteritis.

In the interest of clarity it has seemed much more logical to focus attention upon points of clinical similarity rather than to pursue

the diffusive course of possible differential diagnosis. To this end the suggestion of Meyer[7] is particularly helpful. He pointed out that from among the multiplicity of manifestations, the following were the most conspicuous: "Chlorotic marasmus, polyneuritic and polymyositic symptoms; abdominal symptoms (sense of pressure, bloody diarrhea, vomiting, finally perforation and peritonitis). There is also often rapid pulse and albuminuria." To these dominant manifestations Brinkman[8] added nephritis. Almost without exception the reported cases have shown varying manifestations of obscure sepsis. Yet it does not seem logical to divide the clinical tableau, as have Hutinel and his fellows,[9] into infectious, digestive and cutaneous syndromes. The recent report of Curtis and Coffey[10] offers a sound approach to the diagnostic problem presented by periarteritis nodosa in the analysis of the clinical data after the numerical method of Louis. Unfortunately this review involves only 38 cases as reported in the English language. Of the important data established, the following may be cited: 40% had a febrile course; a like proportion had neuritis and abdominal pain; 24% showed edema; weakness was conspicuous in 21%; and muscular atrophy was noted in 20%. The other clinical manifestations were scattered and did not suggest a specificity.

Much more ambitious was Arkin's attempt[11] to fit the clinical pictures into the four arbitrary pathologic stages which he listed as alterative—degenerative, acute inflammatory, granulation, and healed end stage or scarring. Since the earliest stage is purely microscopic, no characteristic clinical picture is suggested. In the acute inflammatory phase, constitutional symptoms of fever, chills and leukocytosis may be anticipated. Eosinophilia may also occur in the circulating blood. The localizing symptoms and signs depend upon the seat of the major pathologic involvement, *viz.*, gastro-intestinal tract, peripheral nerves, heart, kidney and subcutaneous tissue. In the next stage of granulation, wherein healing and thrombosis may lead to vascular occlusion, anemia and cachexia predominate the constitutional picture; but more serious symptoms of renal insufficiency, cardiac failure, abdominal pain, gastro-intestinal ulceration and gangrene, peripheral neuritis, muscular atrophy and disturbances in the endocrine system may develop. With the cicatricial fourth phase, the last named sequences may be progressive, and Arkin subscribes to the diagnostic triad of Meyer as supplemented by Brinkman.

The routine laboratory studies in periarteritis nodosa are not conclusive. Curtis and Coffey[10] relate the occurrence of leukocytosis in 32% of their surveyed group. Eosinophilia occurred in 12% of these 38 cases; but the occasional extremely high levels are more significant. In Curtis and Coffey's case a peak of 77% eosinophils in 19,900 leukocytes was observed. Lamb[12] found 51% eosinophils of a total white count of 20,900 in 1 of his 2 reported cases. The

eosinophils in Strong's[4] patient reached the high level of 79% of 32,000. Schottstaedt[13] reported 32% eosinophils of a total of 15,600 white cells; and Haining and Kimball[14] 33% of 16,700. Taylor and Farley[15] found 72% eosinophils in 25,700 leukocytes. These figures do not exhaust the available information upon this detail, but they suffice to emphasize the importance of the differential blood picture in this disease. It is significant that eosinophilia in the peripheral blood is by no means a constant finding. However, its occurrence must take on an added importance in the diagnosis and the differential diagnosis of periarteritis nodosa.

From a knowledge of the basic pathologic changes, evidences of renal involvement may be anticipated in a certain percentage of patients suffering from this condition; but in this connection it should be stated that there has long been recognized a marked discrepancy in the clinical expression of the disease as compared with the extent and degree of the vascular changes in the several organs. Albumin, casts and red blood cells may be expected in the urine of such subjects in varying quantities from time to time. With ultimate renal insufficiency the retention of protein end-products and the failure of dye elimination may constitute further marks of the vascular encroachment.

The eye grounds should theoretically afford an unusually fertile field of exploration for such vascular changes as occur in periarteritis nodosa. As a matter of fact, this promise is not fulfilled in actual study. Gruber[16] maintains that there occurs only a neuroretinitis albuminurica secondary to renal involvement. Goldstein and Wexler[17] studied the eye of a patient dying from periarteritis nodosa, in which no abnormality had been observed on a single antemortem ophthalmoscopic inspection, and found lymphocytic, monocytic and plasma cell infiltration about the choroidal vessels indicating a more chronic process than was evident in the visceral bloodvessels. They concluded that ophthalmoscopy should reveal scattered whitish foci which might even be mistaken for miliary tubercles. Singularly, no such findings have been reported in the literature. Strong[4] reports puffiness of the eyelids, blurred optic disks and peripapillary edema. One of Goldstein's[18] patients suffered ablatio retinæ and scleritis. Taylor and Farley[15] report diplopia, elevation of the optic nerve heads and retinal hemorrhages in their case. Pallor and white exudate in the retina appeared in Wever and Perry's patient.[19]

The intra-vitam diagnosis of periarteritis nodosa has been reported in 31 instances,* in several of which there apparently existed some reasonable doubt prior to the necropsy. It may profit to investigate the grounds upon which these clinical diagnoses were made. First, there may be grouped those 14 cases diagnosed from

* The case of Morowitz cited by Gruber is not included, since the reference is not accessible. The diagnosis was apparently made upon the biopsy of a nodule.

their clinical aspect and course. The second case of Kussmaul and Maier[2] was diagnosed by its similarity to their earlier one, and this diagnosis was confirmed by the characteristic appearance of the arteries in a biopsy of voluntary muscle. Kopp[20] recognized the clinical picture in his patient through the tetrad of Meyer and Brinkman. Biopsy of a subcutaneous nodule clinched the clinical impression. Both of Goldstein's[18] cases were diagnosed by their characteristic course and findings. In one the typical vascular changes were later revealed in the arteries of an amputated leg, while in the second a biopsy of the subcutaneous nodules was confirmatory. In the case of Hutinel, Coste and Arnaudet[9] the course was suggestive and a biopsy of the skin fixed the diagnosis. The conclusion of periarteritis nodosa was reached without the support of a biopsy in the cases of Sacki,[21] Bansi,[22] Gohrbandt,[23] Silbermann,[24] Carr,[25] Herrman,[26] and Stepp.[27] In the case reported by Rothstein and Welt,[28] a biopsy of the voluntary muscle failed to confirm the diagnosis, but the necropsy evidence was conclusive. Serious doubt is expressed in the diagnosis of von Spindler's[29] case, in that neither adequate clinical evidence nor histologic support is offered for the conclusion of periarteritis nodosa. Necropsy evidence has been offered in the other instances of an intra-vitam diagnosis without biopsy support.

The larger group of intra-vitam diagnoses of this unusual condition (17 cases) have been incidental to the more exhaustive study of obscure illnesses by biopsy. In a considerable proportion of this series both the biopsy investigation and the revelation of the vascular origin of the ailment have been candidly attributed to chance. As would be anticipated, the subcutaneous nodules have offered the most common point of attack for this diagnostic approach (9 cases). Schmorl,[30] Benedict,[31] von Haun,[5] Weigeldt,[32] van Paassen,[33] Macaigne and Nicaud,[34] Lindberg,[35] Schottstaedt,[13] and Grill[36] have recorded cases of periarteritis nodosa in which the intra-vitam diagnosis was rendered possible through the biopsy of accessible subcutaneous nodules. Since Kussmaul and Maier first determined the diagnostic availability of the biopsy of the voluntary muscles, one would anticipate its wider utilization than in the 2 reported instances of Carling and Braxton Hicks[37] and of Taylor and Farley.[15] In the former a "lumpiness" was observed in the sural muscles and a biopsy revealed the existence of periarteritis nodosa, while in the latter a suspicion of trichinosis lead to a biopsy of the muscle.

The approach in the remaining scattered group of 6 cases of periarteritis nodosa in which the diagnosis was made upon the tissues removed during an operative procedure, may even more clearly be defined as intra-vitam recognition by chance. Manges and Baehr[38] report an instance in which the surgeon (Buerger) recognized the vascular lesions during an exploratory operation.

The diagnosis was confirmed by a biopsy of the mesentery. Gruber[39] diagnosed this condition from the histologic study of the gall bladder removed surgically. Friedberg and Gross[40] and Druss and Maybaum[41] have placed on record instances of periarteritis nodosa recognized by biopsy of the appendix. Much more bizarre are the circumstances under which the diagnosis was made in the cases of Keegan[42] and Gagstetter.[43] In the former a vague history of sepsis and right renal localization led to a nephrectomy. The excised kidney was studded with tiny white nodules grossly resembling miliary tubercles, but to microscopy showing "an acute and subacute obliterating arteritis limited to the arcuate arteries." Gagstetter's patient showed the characteristic lesions in the vas deferens, which was removed subsequent to a prostatectomy.

Renewed interest in the diagnosis of this unusual condition was aroused by the following patient:

Case History. CASE 1.—H. T., aged 48, a farmer, was first admitted to the Wisconsin General Hospital on December 2, 1934, with the chief complaint of "pain in the stomach,' which the patient dated to October 1, 1934. At that time attacks of sour stomach and gaseous distention occurred after meals. The actual discomfort persisted from one meal to the next and there was no apparent relation to the type of food taken, except that sour foods seemed to aggravate the condition. After an initial period of 2 weeks' discomfort, there was a season of freedom from these symptoms until about November 15, 1934, when they recurred in the same order and were accompanied by pain in the epigastrium. This pain, which radiated about the costal margin and to the right groin, occurred immediately upon the taking of food and was absent when the stomach was empty. It had become progressively worse. The appetite was poor; flatulence was marked; nausea without vomiting was experienced. Diarrhea succeeded the medication prescribed by his physician. The stools were tarry on November 30, and on December 1 he passed a small amount of red blood in the stools. A cholecystotomy had been performed in 1931 for somewhat similar symptoms and the only relief experienced by the patient was a freedom from the biliousness that occurred before the operation.

The inventory by systems added the occurrence of steady frontal headache over the past 2 weeks accompanied by vertigo and respiratory difficulty, which had abated with the onset of the gastro-intestinal complaints. During the so-called asthmatic attacks, the patient expectorated as much as a pint of yellowish sputum per day. A backache had been remarked concurrently with the epigastric pain and there were frequent muscle spasms in the legs. The feet had been cold and there had been a steady, dull ache in the feet since the time of the operation. Paresthesias, especially numbness, were noted in the fingers about a week ago. A weight loss of 15 pounds from an average weight of 160 pounds had occurred in the last 2 or 3 weeks. The past medical history is significant in the incidence of the common childhood diseases; measles, mumps, chicken pox and whooping cough. Tonsillitis had also occurred. Cholecystotomy was performed in June, 1931, and some nasal operation for the relief of asthma in 1930. The social history was irrelevant except for the fact that the patient was a farmer. Family history revealed Bright's disease as the cause of death in the father.

Physical Examination. The patient was poorly nourished and showed evidence of recent weight loss. The weakness was apparent. The feet were cold, while the skin of the body was warm and dry. Tenderness was elicited

over both antra. Parenthetically, the patient stated that while driving to the hospital he had developed a sudden coldness and numbness of the left hand, a sharp pain on the ulnar side of the left hand and in the fourth and fifth fingers, radiating up the ulnar side of the forearm and arm to the shoulder and anterior surface of the left chest. The fundal vessels showed slight thickening. The chest was emphysematous in shape and showed some possible accentuation of the normal apical differences in vibratory phenomena. The percussion note was hyperresonant and the breath sounds somewhat diminished over the entire chest. The cardiac apex was to the right of the sternum in the fifth interspace 7 cm. to right of midsternum, and the cardiac dullness was mapped entirely to the right of the sternum. The mitral sounds were heard entirely to the right of the sternum; the aortic second sound was louder than the pulmonic second. The pulse rate was 84; the peripheral vessels were slightly thickened, and the blood pressure was 122/88. The liver edge was palpable at the left costal margin; the splenic edge was palpable at the right costal margin. Exquisite tenderness was elicited in the epigastrium, especially at the site of the postoperative scar; some tenderness was elicited in the left lower quadrant. There was some inability to adduct and abduct the fingers; he was unable to extend completely the fourth and fifth fingers, adduct the thumb, oppose, abduct or adduct the little finger on the left. An anesthesia was determined over the ulnar side of the left hand on the palmar and volar surfaces and of the fourth and fifth fingers except at the extreme tip of the fourth; there was hypesthesia of the ulnar surfaces of the forearm and the inner surface of the left upper arm and the anterior surface of the chest on this side. The deep tendon reflexes were present and active except for the patellar and Achilles reflexes, which were questionably absent. No paradoxical reflexes were determined at this time.

Laboratory Studies. Urinalysis showed albumin and occasional hyalin and granular casts; hemoglobin, 70%; color index, 0.7; erythrocytes, 4,600,000; leukocytes, 25,100; neutrophils, 51%; eosinophils, 40%, and small lymphocytes, 9%. A gastric analysis 3 days later showed 33 degrees total acid and 13 degrees free acid. Stools showed no ova or parasites. The blood Wassermann test was negative on 2 occasions, the spinal fluid Wassermann once. The gold sol curve was 0121100000, the Ross-Jones and Noguchi reactions were faintly positive, and no cells were found in the spinal fluid. The blood chemistry showed 105 mg. % sugar and 36 mg. % non-protein nitrogen. Repeated examination of the stool grossly and chemically showed no blood. A phenolsulphonephthalein dye output of 80% in 2 hours was noted. The 24-hour specimen of the urine showed no arsenic. The analyses of the hair and nails for arsenic showed normal values. The catheterized specimens of urine from the ureters showed a few pus cells and red blood cells from the left side and many red blood cells from the right. The cultures of these specimens were sterile. Detailed sensitization tests were done for the ordinary pollens, epidermals and foodstuffs without establishing a positive reaction in a single instance. An oral cholecystogram the day after admission showed no positive shadows; and although the shadow of the gall bladder was faint, there was no evidence of functional abnormality. The barium enema showed a complete transposition of the colon, the cecum being in the left lower quadrant, and there was some redundancy without obstructive lesions in the colon. The roentgenograms confirmed the fluoroscopic findings and established the transposition of the abdominal viscera. There was no intrinsic lesion determined. A gastro-intestinal series showed a situs transversus with the pylorus and duodenum on the left side, but there was no suggestive intrinsic defect in the upper gastro-intestinal tract. The Roentgen rays of the chest showed the heart in dextro-position. There was very slight haze at the

right apex without granularity. The hilum shadows were somewhat increased in extent and on the left side there were several large caseo-calcareous nodes. There were several calcific shadows along the left cardiac border. The peribronchial markings were accentuated throughout the lung fields. The diaphragms were rounded and smooth, and the sulci clear. The Roentgen ray of the sinus showed mucoperiosteal thickening in the left antrum and similar but less marked changes in the right antrum. Both ethmoidal areas were diffusely clouded. The frontal cells were extensive and deep but apparently clear. Bilateral pyelo-ureterograms showed partial duplication in the right and the left pelvis showed moderate dilatation. The orthodiagram confirmed the physical finding of a dextrocardia and showed a frontal area of 25% in excess of the predicted, and a transverse diameter 5% in excess of prediction. There was some lengthening of the left auricular salient. The electrocardiograms were taken 2 days after admittance and then after a period of a few more weeks and agreed in the details of normal rhythm, downward Q–R–S complexes in all leads, inverted P_1, Q–R–S_2 deeply notched, Q–R–S_3 notched at the base of downstroke and slightly slurred on upstroke, ST segment slightly elevated in Lead I, T_1 and T_2 flat. The auricular and ventricular rates were 85. The auriculo-ventricular conduction time was 0.14 second and intraventricular conduction time was 0.09 second.

Course. There was a slight febrile rise from the 7th to the 17th day. The temperature never exceeded 101° F. The pulse remained proportional to the temperature elevation, as did the respirations as a rule. After the subsidence of the slight febrile reaction, the pulse remained disproportionately high (84 to 104), even though the temperature went above 100° F. on only 2 occasions in the 29 days of his hospital stay. Proctoscopic examination the day after admission revealed no significant pathologic changes. Washings of the antrum were relatively free of infection. Repeated neurologic examinations revealed the cranial nerves intact. The changes in the left hand and arm persisted. Sensation in all expressions over the hands and feet was reduced and there was slight hypesthesia over the left anterior chest. The knee jerks were established only on reinforcement. There was an absence of the ankle jerks and the radial reflexes. The patient continued to complain of tiring of the jaws upon eating, and dated this back for a period of 10 weeks. Upon occasions the upper abdominal discomfort was relieved by the administration of atropin. This pain recurred and the abdomen was exquisitely tender from time to time. Active peristalsis was heard and there was no vomiting. It was interesting that the leukocyte counts ranged from 12,450 with 33% eosinophils to 32,950 with 72% eosinophils. The lowest eosinophil count on this admission was 0.7% of 21,350 leukocytes on the 9th day. Two days before discharge, or on the 27th day of hospitalization, the count was 60% hemoglobin, 4,360,000 erythrocytes, 16,350 leukocytes, 50% neutrophils, 40% eosinophils and 10% lymphocytes.

The impression of a partial intestinal obstruction was held at this time; but no satisfactory explanation was offered for the persistent eosinophilia. The patient was discharged on the 29th day with an impression of post-operative intestinal adhesions and situs transversus completus, duplication of the left renal pelvis, and idiopathic eosinophilia.

After 18 days at home he was readmitted (January 18, 1935) in a very markedly debilitated condition, with the statement that he was unable to evacuate his bowels. He belched gas continuously, experienced a feeling of fullness, and was unable to drink more than ½ glass of water without nausea. Two days before admission he had vomited a greenish material, but there had been no vomiting before or since that time. Dull to sharp pain occurred in the right upper quadrant whenever fluids were taken.

A week previously the ankles had become very edematous and he was conscious of some fever. Cramps in the legs were noted.

The examination added little to the previous study except from a neurologic standpoint. The patient had obviously lost much ground. The neurologic examination showed no ataxia in the usual test movements. The biceps and triceps reflexes were markedly reduced, as were the right abdominal reflexes. The patellar and Achilles reflexes were reduced. The general muscle tone was very poor. Roughly symmetrical patchy disturbances of tactile and temperature senses were detected in both extremities. It became apparent that there was a bilateral peripheral involvement affecting the muscles of the hands, the right more than the left. The changes in the ulnar distribution were more marked. The right median nerve distribution was more markedly involved than the left. The bilateral involvement from the knees distally with paralysis of the muscles innervated by the peroneal and tibial nerves together with the changes in the reflexes in the arms indicated a rather extensive peripheral neuritic involvement. The peripheral edema became more marked and chemosis of the conjunctivæ was noted. Stupor supervened, acetone appeared on the breath, and the patient succumbed after a second period of 17 days' hospitalization.

In this period of hospital stay several added factors were gathered from laboratory study. Urinalyses regularly showed albumin and many granular casts. White blood cells were apparent from time to time. No Bence-Jones protein was found. The hemoglobin fell as low as 50% and the red blood cells to 3,570,000. The white blood cells ranged from 13,700 to 24,250. The neutrophils predominated and ranged from 62 to 94%, and only on 1 occasion, with the leukocytes at a level of 13,700, was there an eosinophilia (11%). The sputum was negative for tubercle bacilli. The blood glucose on this admittance was 75 mg. % and the non-protein nitrogen 52 mg. %. These figures were sharply altered, advancing steadily to 148 mg. % glucose and 86 mg. % non-protein nitrogen. The creatinin ranged from 1.6 to 1.9 mg. %. The blood chlorids were 345.8 mg. %. The total output of phenolsulphonephthalein dropped to 25% in 2 hours. The total serum proteins were 5.2 and 6 gm. %, but the serum globulin equalled the albumin of 2.6 on the first occasion and then exceeded the serum albumin 3.2 gm. as compared with 2.8 gm. The sugar tolerance test done on the 14th day (3 days before death) showed a normal initial level of 80 mg., but the subsequent curve was quite unusual in that at the end of 1 hour a figure of 150 mg. % was established; 2 hours, 141 mg., and 3 hours, 144 mg. This was interpreted as an unusual diabetic curve. On this second admittance the pulse remained irregularly high; but the temperature never exceeded normal level and as a rule was subnormal.

When this patient was seen in consultation (5th day of second admittance) the clinical course, fever, polyneuritis, polymyositis, epigastric pain and eosinophilia led to the diagnosis of periarteritis nodosa. The subsequently advancing evidences of renal insufficiency seemed to clinch this conclusion, and added to these signs of widespread vascular encroachment came the significant sugar tolerance curve. In the absence of the typical subcutaneous nodules, a biopsy of the gastrocnemius muscle was made 6 days before death. No characteristic lesions were determined in these sections.

Autopsy (February 4, 1935; Dr. J. C. McCarter; 3 hours after death). The body is that of a well developed, poorly nourished white male about 40. An old healed upper right rectus incision which admits of some herniation is present. Well marked muscular atrophy of both legs is noted, as well as slight atrophy of the shoulder girdle and manual interosseus muscles. On opening the body cavities a complete situs transversus of the viscera is encountered. The peritoneal cavity contains some excess free fluid and many dense, fibrous adhesions about the gall bladder, the cecum, and the

pelvic portion of the small intestine. About the latter site there is also some fibrinous exudate. There are fibrous adhesions and about 800 cc. of fluid in either pleural cavity. The pericardium is universally adherent by fine, fibrous bands, with pleuro-pericardial adhesions on the right and some calcification. The heart weighs 420 gm. The muscle shows some scarring. On the posterior leaflet of the mitral valve in the line of closure are encountered two small, chronic, rheumatic vegetations. The lungs show apical scars, bronchopneumonia and congestion. The liver has a prominent nutmeg appearance. The gall bladder has a thickened wall and contains a number of stones under 2 mm. in diameter. The stomach mucosa contains numerous petechial hemorrhages. A segment 8 cm. long of the ileum is undergoing gangrene. The kidneys weigh 140 and 150 gm. Their surface is coarsely nodular, and the cut surface shows poor differentiation and obliterated and distorted markings. There are many patches of yellow scarring, and several small infarcts are noted. The intima of the aorta shows a few yellow plaques. No gross lesion of the brain is noted.

The gross *anatomic diagnoses* were: Situs transversus; fibrous pericardial adhesions; cardiac dilatation and hypertrophy; myocardial fibrosis; chronic rheumatic endocarditis; bronchopneumonia; pulmonary congestion and edema; fibrous pleural adhesions; apical pleural scars; hydrothorax, hydroperitoneum, dependent edema; fibrous peritoneal adhesions; acute gangrenous enteritis; chronic cholecystitis and cholelithiasis; chronic passive congestion of liver; atrophy of spleen; multiple renal infarcts; vascular scarring of kidneys; fibrous thickening of left ureter; abdominal incisional hernia.

Microscopic Examination. Many of the smaller arteries and arterioles show a marked intimal fibroblastic proliferation with near-occlusion of the lumina, and in some instances canalization. There is fibrosis of the media, and marked wide perivascular scarring. A sparse infiltration of the walls of the vessels and perivascular tissues with lymphocytes, plasma cells and eosinophils is present. In many of the sections, especially in those of the heart, there are cells in the exudate which bear a high resemblance to Aschoff cells. The vessels of the following organs are affected: Kidneys, heart, stomach, gall bladder, gut, urinary bladder, pancreas, adrenals, voluntary muscle from the leg, and brain. There is some thrombosis in the intestinal vessels, and a gangrenous intestinal wall. Only an occasional small artery in the brain is affected. The gall bladder section shows in addition an acute ulceration of the mucosa.

Additional diagnoses included: Periarteritis nodosa; acute ulcerative cholecystitis.

Two further cases occurring on other services in the Wisconsin General Hospital are cited to emphasize the difficulties in the diagnosis of periarteritis nodosa.

Case Reports. CASE 2.—D. L. B., aged 69, was a white, male, retired merchant. The history was obtained from a son-in-law, since the patient's mental condition did not render the same reliable. For 3 months prior to admittance (June 11, 1929) the patient's mind had been failing. He would begin a sentence and then would be unable to complete it. Delusions of persecution were expressed and apparently these troubled the patient greatly. Although usually good natured, he became quite restless. The appetite had been good until recently. For the past few days the patient had been rubbing his head as if there might be pain, although no spontaneous complaint of this order had been volunteered. Several years ago the patient experienced some so-called asthmatic attacks and there was a recurrence within recent months with some cough. There has been a pro-

gressive weight loss of some 40 to 45 pounds in the past 3 years. An arrhythmia has existed for the past 2 years. There is a cathartic habit; recent incontinence of urine and feces has occurred. About 2 months ago there was a slight stroke, and later there had been muscle twitching without localization, lasting for hours at a time. The past medical history revealed only the "asthma" above-mentioned and chronic arthritis. A toe was amputated a year ago because of a beginning gangrene. The family history was irrelevant. The social history adds moderate use of alcohol and tobacco.

The physical examination revealed a rather uncoöperative individual. There was a marked arcus senilis; the extraocular movements could not be tested; there was a small amount of purulent material in the conjunctival sacs; the pupils were equal and slightly irregular; the eye grounds showed narrow, tortuous vessels, but there was no hemorrhage or exudate. The patient was edentulous, the tonsils were hypertrophied. The chest was emphysematous in type but no other pulmonary abnormality was established; the heart appeared enlarged to percussion; the second sound at the apex was ringing; there were no murmurs but an irregularity of rhythm occurred from time to time interrupting a regular rhythm; the peripheral vessels were thickened; blood pressure was 190/110; there was some tonal arrhythmia observed. The abdominal examination revealed no abnormality. The skin over the hands and wrists was glossy and deeply pigmented. The right hand was held in flexion and could not be extended. The right arm did not move voluntarily but the left arm and hand were used to accomplish all necessary movements; neither forearm could be extended completely at the elbow. There was pain upon movement of the hips, and the left great toe had been amputated. The biceps reflexes were hyperactive; but the patellar reflexes were definitely reduced and the Achilles reflexes could not be elicited. There were no paradoxical reflexes.

Laboratory examinations included a blood count which showed 76% hemoglobin, 0.7 color index, 4,950,000 red blood cells, 8400 white blood cells with 70% neutrophils, 4% eosinophils, and 26% lymphocytes. Blood Wassermann reaction was negative, the blood chemistry showed 94 mg. % sugar and 41.1 mg. % non-protein nitrogen.

On the 5th day after admission the patient showed a rapid decline. There was much mucus in the throat, the pulse was of poor quality and irregular, and death ensued. The clinical diagnoses were arteriosclerotic cardiovascular disease, myocardial degeneration, hypertension, arteriosclerosis of the brain and cord with dementia.

Autopsy (June 16, 1929; Dr. G. Ritchie; 2 hours after death). The body is that of a fairly well nourished elderly white male. There is limitation of motion in the right elbow to about 135 degrees, apparently the result of a bony ankylosis. There are a few fibrous pleural adhesions on the right. The heart weighs 410 gm.; the coronaries are sclerotic and calcified; the muscle is brown, with many gray streaks. The lungs exhibit emphysema, apical scar, posterior congestion and patchy bronchopneumonia. The spleen is somewhat atrophied. The liver shows a prominent nutmeg appearance. The gall bladder wall is thickened and the mucosa is atrophic with adhering yellow granules. The kidneys weigh 160 and 150 gm., and have a fine uniformly granular surface interrupted by several small cysts; the cut surface shows a cortex about 1 mm. in width, fair differentiation, and obliterated markings. The prostate is somewhat enlarged and slightly boggy. The aorta is tortuous, inelastic, and contains many pearly and yellow plaques and some calcification.

Gross Anatomic Diagnoses. Small granular kidneys; chronic myocardial fibrosis; cardiac hypertrophy; bronchopneumonia; senile emphysema; obsolete apical tuberculosis; splenic atrophy; chronic passive congestion of liver; chronic cholecystitis; hypertrophy of prostate; arteriosclerosis.

Microscopic Examination. More or less throughout the series of sections there are prominent changes in the smaller arteries and arterioles. In these vessels there is prominent hyaline degeneration of the media and intima, replacement of intima by fibroblasts, and wide perivascular concentric scarring. The vessel walls and perivascular tissue show a more or less dense infiltration with lymphocytes, plasma cells, eosinophils, and a few neutrophils. There is a notable difference between the lesions in various vessels, some showing chiefly hyalin degeneration of intima and marked infiltration of media; others showing chiefly the scarring with slight cellular infiltration remaining. The sections of the following organs show these changes: Heart, kidney, stomach, appendix, gall bladder, spleen, aorta, prostate and urinary bladder. (It is regretted that microscopic examination of brain tissue was not made.)

Additional Diagnoses. Periarteritis nodosa; chronic pericarditis; purulent bronchitis; acute prostatitis; interlobular pancreatitis; atrophy of pancreas; chronic cystitis.

CASE 3.—J. P., white male, aged 68, farmer, was admitted to the Wisconsin General Hospital on January 30, 1935, complaining of swelling of the legs. The patient stated that his first evidence of disability dated from October, 1934, when he began to experience a feeling of fullness in the head accompanied by dizziness that come on while shredding corn. Two weeks after this time the feet and ankles were swollen and there was pain on motion. The feet felt peculiar by reason of numbness and stinging. The swelling increased progressively, especially over the past month and involved the legs up to the knees and more recently the hands. A dull, aching pain persisted in the legs. For the past few months there had been a gradual decrease in the acuity of hearing and this sense was suddenly lost about 3 weeks ago. Tinnitis has also been noted. The throat was dry at the onset and until 3 weeks ago the patient would cough up some mucus in the morning. Dyspnea has been apparent on exertion since the onset of the dependent edema. Precordial discomfort had been observed at night from time to time. The history by systems added the occurrence of marked limitation of vision in the left eye succeeding an injury 9 years previously; vision in the right eye had failed, particularly in the past few months. Epistaxis occurred twice in the week before admission. Palpitation and arrhythmia had been noted for a period of 6 months. There were night sweats at the onset of the present illness. The appetite has been very poor for the past 4 months. Belching and sour eructations were noted over this period. Vomiting had occurred during the period of present illness. Nycturia had also been noted. Marked weakness and an inability to walk had led to confinement to bed. There was a weight loss of 20 pounds during the present illness. The past medical history was without pertinent relation except for the accident to the left eye above stated and the laceration of the tendon in the left thumb at about the same time. The social history indicated the moderate use of alcohol and tobacco. Family history added nothing of note except diabetes in the father, who died at the age of 79.

Physical Examination. Marked emaciation and prostration, and loss of tissue turgor. A few macules were sparsely scattered over the body. There was lateral nystagmus. Evidences of failing vision on the right and almost complete blindness on the left were noted; the left lens appeared opaque; the pupils were irregular and did not react to light; the fundal vessels were tortuous and there was silver wiring of the arteries. There was some bony deformity of the left nostril and some dry crusting of blood on this side. Deafness in the right ear was observed, but the hearing on the left was relatively good. The patient was completely edentulous; the tongue was dry and covered with a brownish coat; the pharynx was injected and

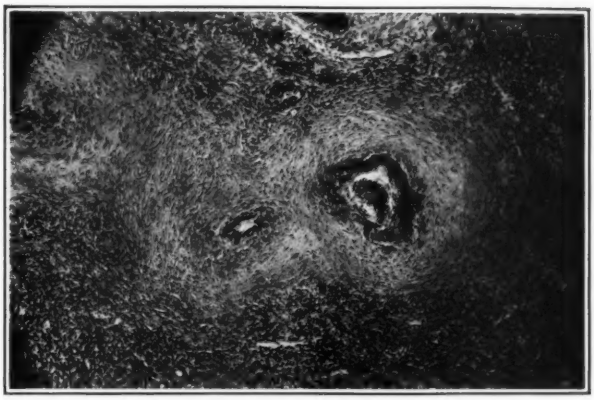

FIG. 1.—Case 1. Arcuate arteries of kidney, showing intimal coagulative necrosis in one, intimal fibroblastic proliferation, greatly reduced vascular lumina, and perivascular infiltration with plasma cells and lymphocytes. (Zeiss apochr. obj. 10, Homal II, × 60.)

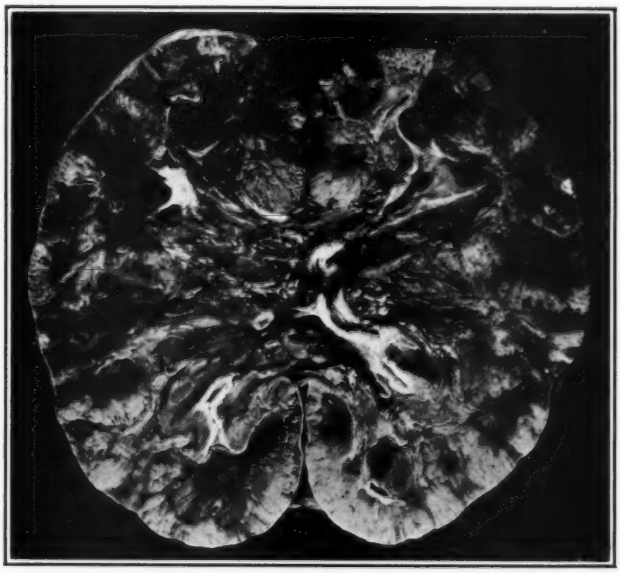

FIG. 2.—Case 1. Cut section of kidney showing generalized intense vascular scarring and infarction. (Reduced from actual size.)

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FIG. 3.—Case 1. Small arteries in heart, showing hyperplastic intimitis, extremely narrowed vascular lumina, perivascular scarring, and sparse cellular infiltration. (Zeiss apochr. obj. 5, Homal I, × 45.)

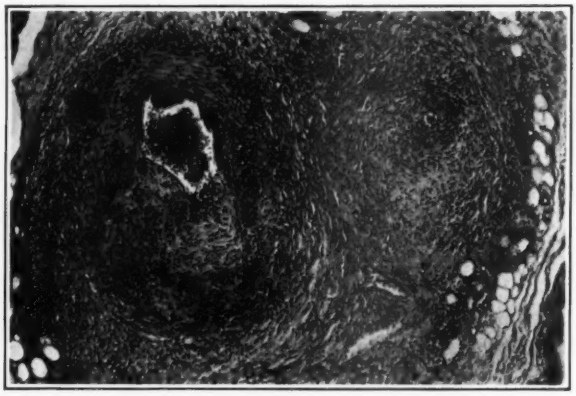

FIG. 4.—Case 1. Small arteries in gastrocnemius muscle, showing hyperplastic intimitis, perivascular scarring and diffuse infiltration with plasma cells, lymphocytes and eosinophils. (Zeiss apochr. obj. 5, Homal I, × 55.)

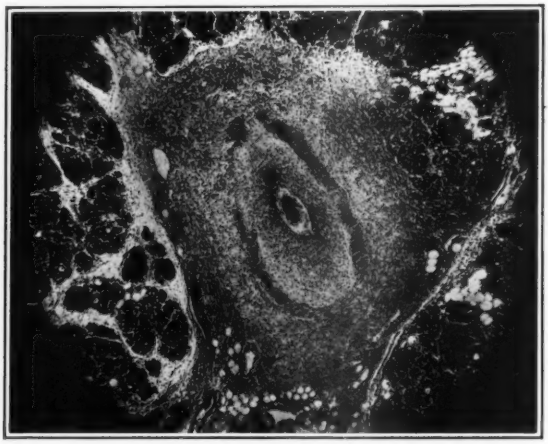

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FIG. 5.—Case 1. Small artery in pancreas, showing marked hyperplastic intimitis and medial and perivascular scarring. (Zeiss apochr. obj. 5, Homal II, × 22.)

strings of pasty mucus hung from the nasal pharynx into the oral pharynx; the tonsils were cryptic and markedly enlarged; the lips were pale and dry. A few palpable cervical lymph nodes were noted. The wasting of the muscles of the thorax was conspicuous. There was some lag in the respiratory movements on the left as compared with the right, and breath sounds were somewhat diminished in the left upper chest laterally. There were fine, moist râles in both bases posteriorly. The heart was apparently enlarged to the left upon percussion; there was a loud systolic murmur at the apex and along the left sternal border and a rough systolic murmur at the base over the aortic area; both aortic and pulmonic second sounds were accentuated. The blood pressure was 206/120. The peripheral vessels were markedly thickened and tortuous. Aside from a palpably enlarged liver no abnormality was established in the abdomen. Marked edema of both legs extended midway to the knees, and edema of the upper extremities as far up as the mid-forearm. Definite diminution of tactile perception was noted in the arms, legs and abdomen. Marked atrophy and loss of subcutaneous tissue was observed throughout. The deep tendon reflexes were normal in the upper extremities except for reduced radials; the abdominal reflexes were reduced; the knee jerks were definitely reduced and the Achilles reflexes absent; no paradoxical reflexes were established. Much pain was evinced upon rectal examination; the prostate was large and soft.

Laboratory Examinations. Urinalysis: Specific gravity ranged from 1.010 to 1.012, a trace of albumin, many coarsely granular casts and, in one specimen, a trace of blood by the benzidin reaction. Hemoglobin, 45%; color index, 0.6; red blood cells, 3,560,000; white blood cells, 10,150; neutrophils, 88%; small lymphocytes, 11%, and large mononuclears, 1%. The blood Wassermann was negative; on admittance the sugar was 113 mg. %; non-protein nitrogen 90 mg. %, and creatinin 2.4 mg. %. Eight days later the non-protein nitrogen had risen to 122 mg. %, and the creatinin to 2.6 mg. %. The phenolsulphonephthalein output was 15% in 2 hours. The total serum protein on admittance was 5.1 gm. per 100 cc.; the serum albumin was 2.37 gm., globulin 2.73 gm. %. Eight days later the total serum protein was 5.5 gm. %, the albumin 2.5 gm. %, the globulin 3 gm. %. The electrocardiogram the day after admittance showed normal rhythm, slight slurring of the *Q–R–S* complexes in Leads I and III, low T_1 and T_3. The intraventricular conduction time was 0.1 second and the auriculoventricular conduction time was 0.17 second.

The course during his hospital stay was complicated by a swelling over the right parotid gland with an area of inflammatory edema, sharply demarcated from the surrounding structures. There was no febrile reaction, although the pulse rate was accelerated. The leukocytes rose to 20,700 with 80% neutrophils, 13% small lymphocytes, and 7% large mononuclears. The absence of local erythema and the rapid resolution of the process argued against a diagnosis of erysipelas. On the 8th day of the hospital stay there was a sharp accession in the respiratory rate with an evident slump in the general condition of the patient, which taken with the presence of many fine, moist râles in the right apex, led to an impression of bronchopneumonia. In spite of supportive treatment, the patient rapidly went on to a fatal termination with advancing cyanosis and a failing circulation.

The clinical diagnoses were arteriosclerotic cardiovascular-renal disease, cardiac enlargement, myocardial degeneration, relative mitral insufficiency, atherosclerotic aortitis, hypertension, functional capacity IIb; nephrosclerosis of arteriosclerotic type with renal insufficiency. The other diagnoses were irrelevant.

Autopsy (February 9, 1935; Dr. G. G. Stebbins; 2 hours after death). The body is that of a poorly developed and nourished elderly white male.

There is some edema of the ankles and flanks. The peritoneal cavity contains about 100 cc. of clear amber fluid. The cecum is displaced and lies under the gall bladder, and the colon first descends and then ascends to become the transverse colon. There are fibrous pleural adhesions at the right apex, and the cavity contains 750 cc. of clear fluid. The left pleural cavity is obliterated by fibrous adhesions. The heart weighs 325 gm. and shows sclerosis of the coronaries, commissural adhesions of the aortic cusps and scarring of the muscle. The lungs are congested and edematous, and bronchopneumonia and an apical scar is present. The spleen has some sugar crust thickening of the capsule. The liver cut surface is nutmeg. In the jejunum and ileum there are dark hemorrhagic mucosal patches, some of which are definitely ulcerated. The largest of these is 7 by 2.5 cm., and the serosa opposite shows some plastic exudate. The kidneys weigh 160 and 150 gm. The capsule strips easily, leaving a smooth, irregularly mottled, yellow and reddish-purple surface; and the cut surface shows obliterated differentiation and markings, with a considerable amount of irregular proliferative change. The aorta has a moderate amount of senile sclerosis.

Gross Anatomic Diagnoses. Arteriosclerosis; myocardial fibrosis; chronic passive congestion of the liver and spleen; pulmonary edema, congestion and atelectasis; hydrothorax; ascites; ankle edema; bronchopneumonia; perisplenic fibrosis; ulcerations of small intestine; fibrous pleural adhesions; emaciation.

Microscopic Examination. The smaller arteries and arterioles in many tissue sections show a coagulative and hyalin necrosis of the media, a prominent fibroblastic proliferative intimitis, and an infiltration of the media, adventitia and perivascular tissue with neutrophils, eosinophils, lymphocytes and plasma cells. Many of the vessels are nearly occluded by the intimitis, and vessels in the intestinal wall show thrombosis. Vessels in the following organs are affected: Heart, kidneys, stomach, gall bladder, small intestine, spleen, urinary bladder, aorta and adrenals. The changes in the heart vessels are not prominent.

Additional Diagnoses. Periarteritis nodosa; thrombus in a pulmonary artery; vascular nephritis.

The etiology of periarteritis nodosa is unknown. Many surmises have been made, and some experimental work has been done, but as yet the pathologic characteristics of the disease seem to lend the surest guides as to the underlying cause.

Earlier writers often mentioned syphilis as the etiologic background; but since the development of the Wassermann reaction for diagnosis and the modern methods of treatment, any connection of the Treponema pallidum with the disease has been repeatedly disproved. Mechanical causes and parasites have been ruled out as etiologic agents; and the possibility of streptococcic septicemia has been disproved by repeatedly negative blood cultures.

There has been bacteriologic examination of the involved tissues and the blood of patients suffering with periarteritis nodosa by a number of workers from time to time, with uniformly negative results. The reports of Lamb[12] and Klotz[3] in this connection are especially interesting. Von Haun in 1920[5] believed that he had produced suggestive lesions in guinea pigs by injection of blood from a patient with periarteritis nodosa. In 1922 Harris and Friedrichs[44,45] claimed to have transmitted the disease to rabbits by

material from lesions passed through a Berkefeld filter. Other workers have not been able to repeat their work, and indeed their published results are not convincing. However, Arkin[11] and Haining and Kimball,[14] as well as some other recent writers incline to the belief that periarteritis nodosa is a specific disease entity, and offer a filterable virus as the probable etiologic agent, even though all attempts at isolation have failed to the present time.

In 1923 Ophüls[46] made a strong plea for the relationship of periarteritis nodosa and rheumatic fever, emphasizing clinical, pathologic and bacteriologic evidence. His summary of the evidence is excellent, and since that time strong confirmatory work has added strength to his position. The presence of lesions in smaller arteries in cases of acute rheumatic fever has received increasing comment; von Glahn and Pappenheimer[47] report "typical" lesions of this kind in 10 out of 47 cases of rheumatic fever which they reviewed. They believe that these lesions are to be distinguished from those of periarteritis nodosa, but the differential points quoted by them do not seem to us to be diagnostic. Friedberg and Gross,[40] in reviewing 8 cases of periarteritis nodosa, have shown the presence of typical Aschoff bodies in the myocardium in 4; and state that they believe that rheumatic fever is a common cause of periarteritis nodosa. They also comment, as have other authors, on the relationship of rheumatic fever, periarteritis nodosa and the malignant nephrosclerosis of Fahr to each other; and they offer as an explanation of "abdominal rheumatism" the lesions of periarteritis nodosa. One of the most recently reported cases of periarteritis nodosa[48] occurred in a patient suffering acute chorea, who was treated with salicylates, and in whom postmortem examination revealed acute myocardial and endocardial rheumatic lesions as well as those of periarteritis. The most consistently reported lesions accompanying periarteritis nodosa are those of rheumatic fever. In view, therefore, of the considerable evidence from many sources of the clinical, pathologic and bacteriologic relationship of rheumatic fever and periarteritis nodosa, the suggestion seems warranted that the latter be placed in the "rheumatic group."

Our cases of periarteritis nodosa exemplify certain of the problems in the clinical and pathologic definition of the disease. All 3 were males. This sex predominates in all reported groups. The age incidence covers a wide range, 3 months to 71 years; so that the ages of these patients, 48, 68 and 69 years, are scarcely significant. The duration of the terminal illness is difficult to fix. Curtis and Coffey[10] give the range from 6 days to 6 years with an average of 16 months, but express the opinion that this figure is too high and favor Strong's[4] figure of 5 months or Gruber's[39] of 4.7 months. The first patient of this group lived slightly over 4 months from the onset of symptoms, the second 3 months, and the third 4 months.

The intra-vitam diagnosis was rendered possible in Case 1 after a continued period of study by the complete evolution of the tetrad

of Meyer[7] and Brinkmann.[8] Vague to sharply localizing epigastric pain, headache, fever, polyneuritic and polymyositic manifestations were the earliest clues. Thereafter came the clear evidences of advancing renal involvement. A further interesting development was the occurrence of a diabetic sugar tolerance curve indicating pancreatic encroachment. The extreme eosinophilia in the differential blood picture was a further focusing detail. In this patient, as well as in Case 3, there was an inversion of the albumin-globulin ratio in the serum protein determinations. The clinical diagnosis was not made in Cases 2 and 3, and clearly the difficulties were much more serious than in Case 1. However, weight loss was an even more conspicuous manifestation in these two than in the first patient. In Case 2 the picture was that of central nervous system deterioration and the etiology was deemed to be simple arteriosclerosis, while in Case 3 renal insufficiency dominated the situation but distinct indications of a polyneuritis and possible polymyositis were overlooked or minimized. Arterial hypertension was added in the last case to direct attention more exclusively to the renal factor, a position supported by the laboratory evidences of renal incompetency. The latter 2 patients showed no such significant eosinophilia as in Case 1 during short periods of hospitalization. Subcutaneous nodules were not detected in any of the three and, as stated before, a biopsy of voluntary muscle in Case 1 was not diagnostic.

Without a clear insight into the etiology of periarteritis nodosa, treatment must be empiric. The experience of Carling and Braxton Hicks[37] and Schottstaedt[13] in the response of such patients to arsphenamin must be unusual. Of course it need not be assumed that lesions responding to arsenicals are syphilitic; but the first named case did have associated syphilis. The trial of arsenicals is advocated without evidence of their specific value, even though many suggest their use only in the presence of recognized syphilis.

Lacking an accepted etiologic agent and specific therapy, the natural evolution of the disease attracts the attention. Many have assumed *a priori* that periarteritis nodosa is of necessity a fatal disease. Its clinical obscurity and the regularity of widespread histologic lesions at necropsy have supported this opinion. Carr[25] has ably analyzed this phase of the question, and Arkin[11] has traced the pathologic steps in the progression of the disease. Spiro[49] refers to clinically latent and pathologically obsolete periarteritis nodosa. Klotz[3] suggests the oversight of many cases through recovery. Schmorl[30] reports a case of the disease diagnosed by biopsy of a subcutaneous nodule that underwent a remission with antisyphilitic treatment. Two years later necropsy revealed only small fibrous foci in the kidneys, liver and heart as residuals of the earlier periarteritis nodosa. Probably the most unusual observation upon the evolution of the disease is that of Keegan[42] previously cited. A right nephrectomy had been performed under conditions sug-

gesting a renal infection. The removed kidney presented arteriolar changes characteristic of periarteritis nodosa. Renal and circulatory incompetency succeeded this operation, and at necropsy 2 months later similar changes were observed in the cystic artery of the gall bladder, the pancreatic and the splenic arteries. The remaining kidney had undergone transformation to early arteriosclerosis and chronic vascular nephritis. This experience led Keegan to postulate that many cases of chronic vascular nephritis may have their origin in mild renal periarteritis nodosa.

Summary. From this review of the subject certain deductions regarding periarteritis nodosa seem reasonable:

1. The incidence of the disease probably greatly exceeds its recognition clinically and pathologically.

2. The pathology consists of a necrotizing arteritis, subacute and chronic cellular and fibrinous exudation, aneurysm formation, thrombosis, and fibroblastic proliferation and repair. The smaller arteries and arterioles are affected; and degeneration and infarction in the areas of supply are common.

3. Etiologically periarteritis nodosa is probably closely associated with the "rheumatic group" of diseases.

4. The tetrad of Meyer and Brinkmann, chlorotic marasmus, polyneuritis and polymyositis, striking abdominal manifestations (cramps, vomiting, diarrhea, melena and perforation) and nephritis, offers a logical foundation for the clinical appreciation and diagnosis of periarteritis nodosa.

5. Unexplained fever, polymyositis, polyneuritis and eosinophilia constitute peculiar grounds for the consideration of this diagnosis.

6. Wherever the question arises, recourse should be had to biopsy of accessible nodules or voluntary muscle.

7. Further study may grant diagnostic values to ophthalmoscopy, electrocardiography[50] and roentgenography of the lungs[26] in periarteritis nodosa as yet not clearly established.

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(Titles have been omitted for sake of brevity.)

PERIARTERITIS NODOSA (NECROTIZING PANARTERITIS) IN CHILDHOOD WITH MENINGEAL INVOLVEMENT.

Report of a Case with Study of Pathologic Findings.

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Since periarteritis nodosa is comparatively rare in adults, and particularly so in children, we have thought it worth while to report the following case which presents a number of interesting and

unusual features. A review of the literature of periarteritis nodosa in infancy and childhood was made by Rothstein and Welt,[1] in 1933, who abstracted 21 cases and added 2 cases of their own. In the same year, Nowak[2] reported an additional case in a child aged 12, and recently Friedberg and Gross[3] have reported 2 cases associated with rheumatic fever in children, 1 of which had been previously reported by Rothstein and Welt.

Case Report. *History.* An Italian schoolgirl, aged 9, was admitted to the Long Island College Hospital on January 28, 1933, because of a purplish discoloration of the left ankle, pain in both legs, loss of weight and fever.

Six weeks before admission she injured her left ankle by striking it against a hard object. There was no discoloration, no swelling and no pain at that time. She was perfectly well until January 8, 1933, 20 days after the injury. She then complained of chilliness and pain in both legs. Her temperature was 102° F. by mouth. The next day she was unable to stand or walk because of the pain and remained in bed. She could move both legs but the motion was painful. These symptoms continued, and 7 days before admission the mother observed a small purplish discoloration on the outer surface of the left ankle. The discolored area gradually increased in size without any perceptible swelling. The pain in the legs became progressively worse and was most marked in the thighs and in the region of the left ankle. It was so severe that she was unable to sleep. She refused food but took liberal amounts of fluid without vomiting. The temperature fluctuated between 100° and 104° F. Because of the fever, loss of weight, pallor and the severity of the pains, she was brought to the hospital for treatment.

The father, mother, 5 brothers and sisters were living and well. The mother had had 2 miscarriages, apparently spontaneous. During infancy the patient had been poorly cared for. No cod-liver oil had been given during this period. At the age of 4 she developed pertussis of average severity. She had several colds each winter, with no complications. There was no history of tonsillitis, chorea, growing pains, arthritis or scarlet fever. The mother stated that she was backward at school.

Physical Examination. The temperature was 103.8° F., pulse 106 and respirations 28 per minute. The child was acutely ill, pale and apparently in severe pain. She was restless and irritable. There had been considerable loss of weight. She rested on her side with the lower extremities drawn up against the abdomen.

The skull showed no abnormalities. The eyes were somewhat sunken. The pupils were equal and their reactions normal. The ears were normal. There were herpetic lesions on the lower lip. The mucous membranes of the nose and mouth were pale, the tongue was coated and dry and there were many carious teeth. The tonsils were small and the pharynx was reddened but no exudate was noted. There was no enlargement of the cervical lymph nodes. The chest was symmetrical and narrow. The lungs were apparently normal. The heart sounds were regular and strong and there was no evidence of enlargment. A soft, apical systolic murmur was present but was not transmitted. The abdomen was flat and showed a moderate degree of generalized tenderness and rigidity. The liver and spleen were apparently normal in size. No abnormal masses were palpable. The external genitalia were normal.

The upper extremities were normal, the lower symmetrical and there was no edema. The veins of the ankle and dorsal surface of the left foot seemed more prominent than is usual in a child of this age. To a lesser extent this was also true of the right extremity. Any attempt passively to move

the lower extremities was accompanied by severe pain. The joints seemed to be normal. Pain was elicited when pressure was applied to the thighs. An extremely tender, not elevated ecchymotic area, about 4 cm. in diameter, was found over the external malleolus of the left ankle. The reflexes were equal and active on both sides. No pathologic reflexes were elicited.

Laboratory Data. The red blood cell count was 4,240,000 per c.mm., and the hemoglobin was 54% (Sahli). There were 20,500 white blood cells per c.mm., with 83% neutrophils, 13% lymphocytes, 2% mononuclear and 2% eosinophils. The bleeding and coagulation times were normal. The platelets numbered 230,000 per c.mm. The blood and spinal fluid Wassermann reactions were negative and the spinal fluid cytology and pressure were within normal limits. Non-protein nitrogen and sugar determinations of the blood were normal. The blood culture and Widal reactions were negative. A roentgenologic study of the left ankle, pelvis, hip joints and lower spine showed no abnormalities.

Course. The course of the child's illness was that usually seen in general sepsis. The temperature fluctuated between 101° and 104° F. The pulse continued regular but very rapid. There was no change in the systolic murmur. Generally, except for loss of weight, the physical findings did not differ from those elicited at the initial examination. However, 8 days after admission the ecchymotic area on the left ankle increased to about 6 by 4 cm. in size. Several small ecchymotic areas also appeared on the ankle, dorsum of the left foot, the inner surface of the left leg and the plantar surface of the right foot. Several blebs contained a serosanguineous fluid developed on the skin of the left ankle over the largest of these lesions. Culture of this fluid revealed a hemolytic Staphylococcus aureus. Two days after their appearance the blebs ruptured and left an ulcerated area from which a serosanguineous fluid continued to exude. There was now a loss of pain and temperature sense distal to the ecchymotic area on the left ankle, while directly over this area these sensations were diminished. Treatment did not change the appearance of these lesions.

Two weeks after admission laboratory studies revealed a red blood cell count of 3,900,000 per c.mm. and a hemoglobin of 65% (Sahli). The white blood cells numbered 19,200 per c.mm., with 84% neutrophils and 16% lymphocytes. The urine showed a trace of albumin, a few pus cells but no red blood cells and no casts. Repeated blood cultures continued to show no growth.

Despite supportive and symptomatic treatment the child became progressively worse, and 15 days after admission she developed a clonic convulsion of the left arm and left side of the face, which soon involved the entire body. Spinal puncture showed an increase of pressure, but no changes in the cytology or chemistry of the spinal fluid were found. The systolic blood pressure was 115 mm.; the diastolic pressure could not be obtained. The convulsions ceased the following day and were replaced by a rigidity of the decerebrate type. The patient remained in coma and died 2 days later without regaining consciousness.

The presence of bizarre symptomatology and the absence of definite laboratory findings made the diagnosis of this case most difficult. The opinion was expressed, however, that we were dealing with a widespread vascular lesion of undetermined nature.

Necropsy. The body was that of a fairly well-developed but poorly nourished, white, female child. On the lateral and posterior aspects of the left ankle there was a large ulcerated area, with an ecchymotic border, which measure 8 cm. in length, 4 cm. in width, extending through the superficial fascia to the peroneus tendons (Fig. 1). No gross evidence of infection of this area was noted. In the immediate vicinity there were a few small reddened ulcerated areas, measuring from 5 to 10 mm. in diam-

eter, which were covered by dark red crusts and surrounded by brownish-purple zones apparently subsiding ecchymoses. There was no swelling of the soft tissues, bone or joint in this region. The plantar surface of the right foot showed several small ecchymotic spots, measuring from 2 to 4 mm. in size. No other abnormalities were noted on external examination.

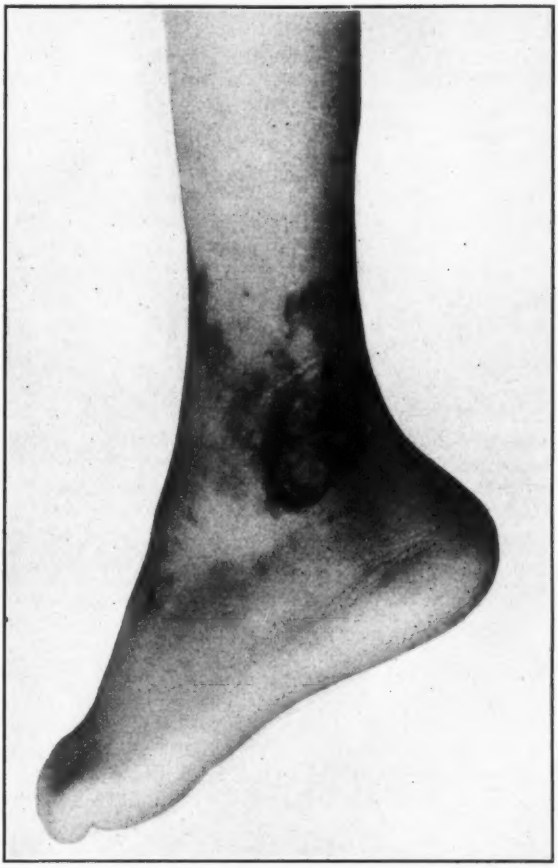

FIG. 1.—Photograph of left ankle, showing ulceration over external malleolus with surrounding ecchymotic areas. The peroneus tendons can be seen in the posterior portion of the ulcer.

Each pleural cavity contained 50 cc. of clear yellow fluid. The surfaces were free of exudate. The lungs showed passive congestion and edema, and their combined weight was 955 gm. No gross lesions of the pulmonary bloodvessels could be found.

The pericardial sac contained 30 cc. of blood-tinged fluid. The pericardial surfaces were smooth and glistening. The heart weighed 250 gm. (normal weight for 9-year-old female, 110 gm.[4]). The myocardium, except for slight hypertrophy of the right ventricle, was essentially normal. On the auricular surface of the anterior mitral leaflet, along the line of closure, a nodular ridgelike elevation, measuring 1 mm. in height, was noted. On

the posterior leaflet there were several grayish-white nodules, measuring from 1 to 2 mm. in diameter. Grossly the appearance was that of a healed rheumatic endocarditis. The remaining valves showed nothing of pathologic significance.

The abdominal cavity was bathed in a greenish-brown, sour-smelling fluid, of which there was 90 cc. in the pelvis. The serous surfaces were found covered with a fibrinous exudate. On the lesser curvature of the stomach, 2 cm. from the pylorus, there was a perforated ulcer, measuring 1 cm. in diameter. Another small ulcer, but non-perforating, was found at the pylorus and still another in the first part of the duodenum. The remainder of the gastro-intestinal tract was normal except for several small petechial hemorrhages in the mucosa of the transverse colon and lower ileum.

The liver was about normal in size, weighed 540 gm. (normal weight, 750 gm.[4]) and was reddish-brown in color. The surface presented numerous irregular depressed yellowish areas, surrounded by hemorrhagic zones. These areas almost entirely covered the superior and inferior surfaces of the left lobe. On section, areas similar to those seen on the surface were found, and in the portal areas there were numerous small gray translucent nodules resembling tubercles. The vessels in the portal canals were unusually prominent and markedly thickened, the lumina of some being almost completely occluded. In some instances thrombi were found in the vessels.

The spleen was about normal in size and weighed 70 gm. (normal weight, 60 gm.[4]). The capsule was thin and on the surface irregular depressed yellowish areas were found. Similar areas were found on the cut surface.

The kidneys were slightly enlarged and together weighed 145 gm. (normal weight of each, 120 gm.[4]). Their external and cut surfaces presented numerous small yellow patches surrounded by hemorrhagic zones. The interlobular and arcuate arteries were thickened, gaping and in some instances occluded.

The adrenals were essentially normal except for several small pin-point orange-yellow nodules found in both the cortex and capsule.

The pancreas was grossly normal except for a moderate degree of thickening of the vessel walls.

On opening the skull, the dura was found to be normal. The leptomeninges were congested and a slightly increased quantity of opalescent subarachnoid fluid was found. The vessels at the base of the brain appeared normal. The cerebral convolutions were slightly flattened and the sulci somewhat narrowed. Sections through the brain showed no gross pathologic changes. The dural sinuses contained fluid blood and appeared normal.

The pituitary body was normal in size but markedly congested.

In the ethmoid sinus a small hemorrhagic erosion of the mucous membrane was found.

The right eye was removed and found normal in size and shape. The cornea was slightly "steamy," so that no details of the inner structures could be seen. After fixation "windows" were cut in the horizontal plane. The retina was not detached and, moreover, gave the impression of being abnormally adherent. Otherwise the organ appeared grossly normal.

Culture of the blood taken at autopsy revealed no bacterial growth.

Microscopic Examination. The most striking lesions were found in the small and medium-sized arteries of the kidneys, liver and spleen and the superior mesenteric artery. The media of most of these arteries showed both degenerative and inflammatory changes. The mildest changes noted were edema of the media and swelling of the muscle cells. Other lesions apparently more advanced showed a thready fibrinous exudate in both

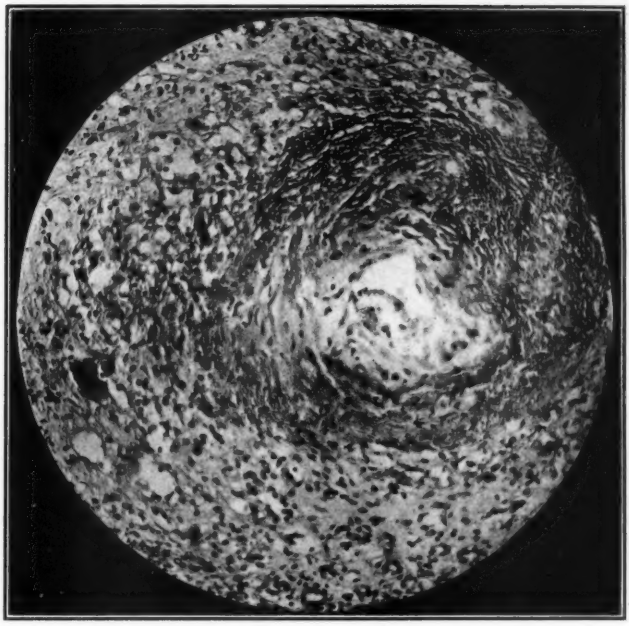

FIG. 2.—Section of small artery, showing destruction of media with hyalinization and infiltration of adventitia and periadventitial tissue with epithelioid cells and round cells. One very large and several smaller Langhans' giant cells are shown.

FIG. 3.—Section of brain and pia-arachnoid in a sulcus, showing congestion, edema and moderately heavy infiltration with round cells. There is marked margination of leukocytes in bloodvessels.

FIG. 4.—Section of margin of skin ulcer, showing two arteries with marked irregular intimal thickening and replacement of media and adventitia with granulation tissue.

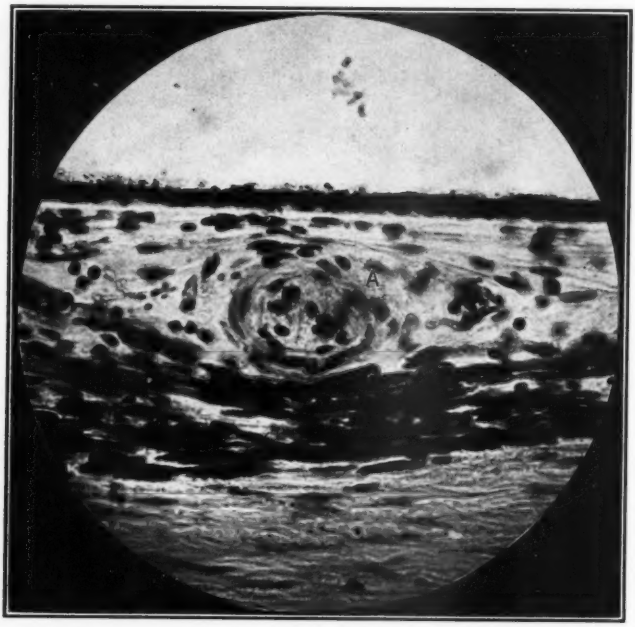

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FIG. 5.—Section of eye, showing vascular changes and cellular infiltration in the choroid. At *A* is seen a small thrombosed artery with many leukocytes in the thrombus. The retinal separation in this region is an artifact.

the inner and outer portions of the media. Arteries more severely damaged showed coagulation necrosis of the media and hyalin degeneration. This necrotic process involved, in some arteries, the intima and adventitia, and in some instances was associated with hemorrhage throughout the entire vessel wall. In many of the arteries the necrotic and degenerated areas were infiltrated with moderately large numbers of neutrophils and lymphocytes and a few plasma cells. In other vessels showing these marked changes saccular aneurysms, measuring from 0.5 to 1 mm., were found, some of which had ruptured, giving rise to perivascular hemorrhages. An almost constant finding was intimal thickening or occlusion of the lumina as a result of intimal proliferation (Fig. 2). In the latter instance it was at times impossible to differentiate proliferated intima from recanalized thrombi except for the presence of blood pigment in the latter. The adventitia of some arteries showed fibroblastic proliferation and, as previously mentioned, was also frequently involved in the degenerative, necrotic and acute inflamatory processes.

The degenerative and acute inflammatory changes in the walls of some of the vessels were associated with the formation of granulation tissue, apparently replacing the necrotic areas. In such lesions the neutrophilic infiltration was less marked. However, in some arteries so involved there was also evidence of recent medial necrosis, in addition to the granulation tissue and intimal proliferation, suggesting acute exacerbations of the process.

An outstanding feature in the histologic examination was the finding of epithelioid cells in the areas of granulation tissue in and around the adventitia of the affected vessels. In many of these areas giant cells of the Langhans type were seen. The giant cells varied in size and contained from 6 to 10 nuclei. These lesions, which resembled granulomata, were most numerous in the kidneys and spleen.

The parenchyma of the liver and kidneys showed generally various stages of epithelial degeneration. Typical infarcts were found which were infiltrated with moderate numbers of neutrophils, lymphocytes and a few plasma cells, and surrounded by hemorrhagic zones. The spleen also showed areas of infarction.

The heart presented a round-cell infiltration of the myocardium, the muscle cells of which showed parenchymatous degeneration. Scattered throughout the myocardium were small irregular patches of edematous connective tissue in which a few necrotic remnants of muscle cells could be discerned. There was a moderate to marked degree of intimal proliferation in the smaller branches of the coronary arteries. Necrosis as well as necrobiotic changes were found in the media and there was an adventitial and periadventitial proliferation of fibroblasts and infiltration of lymphocytes and plasma cells. In the subepicardial fat one of the larger branches of a coronary artery showed a considerable degree of necrosis and round-cell infiltration of the media. In one area this necrosis was extreme, with thinning of the wall and beginning aneurysm formation. The atrial surface of the endocardium of the mitral valve was thickened by edema and connective-tissue proliferation and was infiltrated with lymphocytes. The small arteries in the valve showed perivascular round-cell infiltration and intimal thickening. The vascularity of the valve, however, was considered normal for a child of this age. The cellular infiltration was most prominent at the bases of the small nodular excrescences, noted grossly forming an elevated ridge along the closing margin of the valve. These excresences consisted of hyalinized collagenous fibers, with few fibrocytes, infiltrated with moderate numbers of lymphocytes and covered by a layer of endothelium. No Aschoff bodies were found in the myocardium or valves.

The intima of the aorta showed slight connective-tissue proliferation.

In the media a few scattered light blue staining oval areas of necrosis were found. The vasa vasorum in the outer third of the media were increased in number and presented a perivascular round-cell infiltration and intimal proliferation. The vessels of the adventitia were also thickened, and in some places their lumina were obliterated either as the result of intimal proliferation or thrombus formation. In some areas the adventitia as well as the outer third of the media was infiltrated by lymphocytes and a few plasma cells.

The lungs revealed no pathologic lesions of significance in either the parenchyma or vessels.

Sections of the stomach showed arterial lesions similar to those observed in the liver and kidney. The walls of the perforated ulcer showed necrosis of the entire thickness of the mucous membrane and were also found to be infiltrated with neutrophils, lymphocytes and a few plasma cells. The mucous membrane from various other sites showed atrophy, degeneration or necrosis of the epithelium. The muscularis appeared edematous and showed small areas of degeneration. The serosa was covered with a layer of exudate consisting of fibrin and pus cells.

The duodenum presented an ulcer which extended into the inner portion of the submucosa, the outer half of which showed considerable edema. An acute inflammatory reaction was noted in the tissue surrounding the ulcer. The muscularis and serosa were congested and edematous and the former showed small areas of necrosis. In the subserosal coat a medium-sized artery showed degenerative and inflammatory changes and its lumen contained a recanalized thrombus. Smaller arteries in this region also showed changes similar to those first described.

The pancreas showed nothing of pathologic significance except a moderate degree of arterial intimal proliferation, degenerative changes of the media and perivascular fibroblastic proliferation. No inflammatory changes were found.

The arteries of the adrenal capsule revealed lesions similar to those described in the kidney, liver and spleen. Numerous recanalized thrombi were found filling the lumina of many arteries. The collections of sympathetic ganglion cells showed various stages of degeneration. Focal areas of necrosis were noted in the cortex. The medulla also showed scattered areas of degeneration and necrosis of its cells.

The leptomeninges were edematous, moderately congested and infiltrated with moderate numbers of lymphocytes and plasma cells (Fig. 3). The arteries of the meninges showed degenerative and necrotic changes of the media. The ganglion cells of the cerebrum showed a marked degree of cloudy swelling, eccentricity of the nuclei, chromatolysis, or necrosis with extrusion of nuclei and a slight degree of satellitosis. Small arteries of the brain showed both degenerative and necrotic changes in the media, intimal proliferation and perivascular collections consisting of lymphocytes, a few plasma cells and an occasional neutrophil. There was a considerable degree of edema throughout the brain substance.

The pituitary appeared markedly congested and edematous, and in several areas there were small patches of necrosis, presumably infarcts. The vessels of the surrounding dura showed intimal thickening and an occasional organized thrombus.

Sections through the margin of the ulcer of the leg showed atrophy and necrosis of the epidermis. The corium was edematous and infiltrated with round cells. In the floor of the ulcer a medium-sized artery showed a moderate degree of intimal proliferation, medial necrosis and acute inflammatory infiltration throughout its entire thickness. At one point this artery was ruptured. The smaller arteries showed rather marked intimal proliferation (Fig. 4), degenerative changes in the media and collections

of inflammatory cells in both the media and adventitia. Clumps of bacteria were found in the necrotic material lining the ulcer.

Microscopic examination of eye (Dr. J. A. deVeer): The cornea was found to be the seat of a healing ulcer in which there was irregular regeneration of the surface epithelium, focal destruction of Bowman's membrane and light leukocytic infiltration of the corneal stroma. There was also a subacute and chronic iridocyclitis, as shown by cellular infiltration of the iris and ciliary body with exudation into the aqueous chambers, and synechiæ between the pupillary portion of the iris and the lens capsule. The lens was otherwise normal.

The most marked changes were seen in the choroid, which also was the seat of subacute and chronic inflammation. The vessels here showed thickening of their walls with narrowing or complete occlusion of their lumina. An occasional artery showed a thickened intima infiltrated with neutrophils and lymphocytes. Perivascular mantles of lymphocytes were found about many of the vessels. The choroidal stroma was atrophic and fibrotic, with a light mononuclear and neutrophilic infiltration (Fig. 5).

The attachment of the retina to the choroid was firmer than usual. There were no changes of note in the retinal vessels. The macula was edematous and the fovea centralis atrophic. The optic nerve showed mild inflammatory changes.

There was also a subacute and chronic episcleritis and orbital cellulitis. The arteries and arterioles in these tissues were thickened and in many the lumina were narrowed or occluded.

The eye changes may be summed up as those of subacute and chronic uveitis, episcleritis and orbital cellulitis. The vascular lesions were of the same order as those in other organs, but with less acute degenerative and inflammatory features. The ulceration of the cornea may have been in part or entirely the result of lagophthalmos.

Discussion. The term "necrotizing panarteritis" is suggested as being descriptive of the lesions in this arterial disease and, therefore, preferable to the older designation "periarteritis nodosa." The lesions are not nodose but extend over extensive segments of the affected arteries, as may be demonstrated by serial sections. They are not purely perivascular in location but involve all the coats of the affected arteries as well as the perivascular tissue in an extensive necrotizing process.

The lesions encountered in our case fit well into the classification of Arkin,[5] who divides the disease into a degenerative, an acute inflammatory, a granulation tissue and a healed stage. A few of the vascular lesions in our case were degenerative, some were inflammatory, but the majority were of the granulation tissue stage. We were unable to find any examples of the healed stage. In some instances, apparently because of the rapidity of events and because of acute exacerbations of the process, all three stages were found in the same artery. It is, therefore, impossible to say which coat was the seat of the earliest change. If the presence of a hyalin eosin staining band is to be accepted as characteristic of the initial stages of the vascular lesion, then this zone was found in our case to be located chiefly in the media of the vessels.

The perivascular and adventitial nodules produced by proliferative changes, and containing epithelioid cells, giant cells and round

cells, have a striking resemblance to the infectious granulomata. Ophüls,[6] in his discussion of periarteritis nodosa, refers to these lesions as granulomata, and mentions that Aschoff noted their resemblance to those found in rheumatic fever. The former author stated that giant cells were not found in the nodules but only in the media. In our case, however, giant cells were found in both the nodules and media. Haining and Kimball,[7] in a recently reported case of periarteritis nodosa, have noted the occurrence of numerous giant cells around the affected arteries in the kidney.

The presence of a leptomeningitis in this case is of particular interest, since no instances of meningitis primarily due to periarteritis nodosa have been previously reported. In adults, meningitis has been mentioned in 2 cases. In 1 of these (Haining and Kimball[7]) the meningitis was due to a complicating pneumococcus infection and bore no causal relation to the primary disease. In the other (Bennet and Levine[8]) there were clinical signs of meningitis, but these were not supported by anatomic findings. In several other cases, 3 in children, although there were clinical manifestations of cerebral involvement and meningeal irritation, the lesions found at autopsy were hemorrhage into either the brain or the meninges from rupture of aneurysms or softening of the brain due to thrombosis.

The occurrence of a gastric and a duodenal ulcer with perforation of the former and a resulting acute peritonitis is also of interest, since, in children, no cases with these manifestations have been reported.

Ulceration of the skin in children has been reported in only 2 previous cases (Debre,[9] Hutinel[10]). In these the ulceration appeared, respectively, on the tenth and seventh days of the illness. In our case the ulceration was extensive, involving the deeper portions of corium and superficial fascia with typical periarteritic lesions in the base of the ulcer and surrounding tissues. The fact that the ulceration in this instance was preceded by injury to the involved area, with persistent ecchymosis and deep tenderness, gave rise to clinical suspicions of underlying bone disease.

The relationship of this disease to rheumatic fever has been suggested by several authors, and most recently by Friedberg and Gross,[3] who report the occurrence of periarteritis nodosa associated with rheumatic fever and rheumatic heart disease in 4 cases, 2 of which were in children. These authors, therefore, suggest rheumatic fever to be "a common cause of the vascular lesions, termed periarteritis nodosa." In our case there were lesions on the mitral valve which were interpreted as rheumatic verrucous endocarditis, though no Aschoff bodies were found. Apparently rheumatic heart disease and periarteritis nodosa are not uncommonly associated. Whether or not this is due to causal relationship must be determined by further study.

Opportunities for histologic examination of the eyes in cases of periarteritis nodosa have been rare, and the findings of characteristic arterial lesions in this case in both the bulb and orbital tissue is of especial interest.

It is to be noted that there was a paucity of symptoms referable to the parenchymatous organs when compared to the widespread involvement of these organs, particularly the kidneys.

Summary. 1. A case of necrotizing panarteritis (periarteritis nodosa) in a girl, aged 9, is presented.

2. The widespread vascular lesions correspond to the degenerative, inflammatory and granulation tissue stages of this disease, as described by Arkin.

3. A primary subacute leptomeningitis due to periarteritis nodosa is described. No other cases of primary meningitis either in children or adults have been reported.

4. The occurrence of unusual features, such as gastro-intestinal ulceration with perforation and peritonitis, ulceration of the skin following injury and the occurrence of ocular lesions has been briefly discussed.

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PERIARTERITIS NODOSA WITHOUT PERIPHERAL NODULES DIAGNOSED ANTEMORTEM.

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Although an uncommon condition, periarteritis nodosa is of interest from several aspects. To the clinician, the protean manifestations of the disease are a challenge to his diagnostic acumen.

By virtue of the microscopic resemblance to more frequently encountered conditions such as rheumatic fever and typhus fever, periarteritis nodosa appeals to the imagination of the pathologist. To both groups the problem of the etiology of this almost inevitably fatal disease, is of importance.

The various clinical types of periarteritis nodosa have been described frequently. Nevertheless, an antemortem diagnosis has been excessively rare, and such of these as have been made were usually the result of a biopsy performed to establish the suspected presence of some other disease such as trichiniasis or dermatomyositis. An occasional case has been recognized at operation with the finding of nodules in the abdominal cavity, or again, upon microscopic examination of an excised organ. A correct clinical diagnosis has not been made more often either because of too great emphasis on a single group of findings to the exclusion of other important ones, or else because of the confusion aroused by the multiplicity of bizarre symptoms.

The present report is concerned with a case of periarteritis nodosa without peripheral nodules, in which the diagnosis was suspected and verified by biopsy of a muscle, before death. This is the first instance of such a case thus directly established, that I have been able to find in the American or English literature.

Case Reports. CASE 1.—R. S., a white, male mechanic, aged 44 (Unit No. 51766), was admitted to this hospital on October 14, 1933, complaining of fever, chills and pains in the extremities. His father died at 74 of hypertension; his mother at 70 of a stroke. The patient's general health had been excellent. He had had the usual childhood diseases including scarlet fever. At 25 he suffered a mild attack of pneumonia. In 1923 there had been a traumatic ulcer on the left shin which was slow in healing. In 1931, as the result of a fall, he broke several ribs on the left side. At the age of 20 he had contracted a gonorrheal infection. There was no history of primary or secondary syphilis, but 18 years before he had received an inadequate course of antiluetic treatment: about 12 injections in all. He had 5 living children; his wife had had no miscarriages. His habits were temperate. For several years he had known of an existing hypertension, the systolic pressure sometimes attaining a level of 220 mm.

In January, 1933, he was first seen in the outpatient department where he appeared with the complaint of lumbar pain. He was found to have a blood pressure of 212/114 mm., normal temperature, and a pulse rate of 92. There was a skin eruption, interpreted as lichen planus, over the body. The urine contained a trace of albumin and microscopically, pus cells and bacteria. The Wassermann reaction was positive. Roentgen ray showed no enlargement of the heart or aorta. He was started promptly on antiluetic treatment consisting of alternating courses of bismuth and neoarsphenamin. To this schedule he adhered until October 1, 1933.

The patient dated the onset of his present illness to early September, 1933. Detailed inquiry, however, elicited more remote relevant facts. During the winter of 1930 he had had several transient attacks of numbness and blanching of the fingers of both hands, more marked on the left. He recalled 3 or 4 attacks of amblyopia in the left eye of brief duration in the summer of 1933. On September 7, 1933, he was seized with occipital aching, pains in the shoulders, wrists and lower extremities. There were

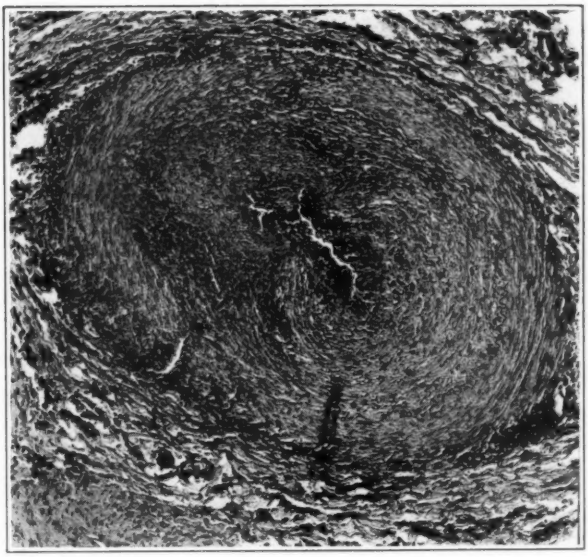

FIG. 1.—Artery in a muscle from Case 1. (× 90.)

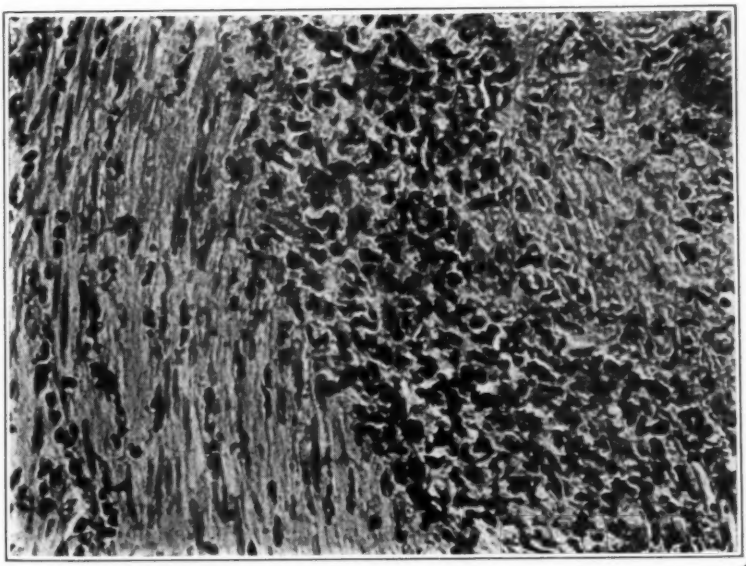

FIG. 2.—Intima and media of same vessel. (× 350.)

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chills and sweats in the following days, with fever as high as 101°. He became weak and lost weight. Just before he was forced to bed, after 3 weeks of continuous distress, his blood pressure had fallen to 140 mm. systolic. Following this the pains disappeared but weakness progressed and he lost about 15 pounds in a few weeks. Bilateral increasing deafness now set in. Three days before admission there appeared numbness and paresthesias of the right hand followed a day later by similar symptoms of the left hand.

On admission, October 14, 1933, his temperature was 103.8°, pulse 108, blood pressure 155/90 mm. He appeared chronically ill. There was conspicuous loss of weight. His hearing was impaired by a disturbance of nerve conduction. The fundi revealed minimal arteriolar changes. Pupils were irregular but reacted promptly to light. Examination of the heart and lungs showed no notable abnormalities. Both the liver and the spleen were just palpable. Over the hands there were areas of hypesthesia, involving the ventral surfaces of both hands as well as the dorsal surface of the right. No motor weakness was made out. Reflexes were normally elicited save for the abdominals and cremasterics.

The erythrocyte count was 4,340,000; hemoglobin 80%; leukocyte count 13,300; neutrophils 91%, eosinophils 3%, lymphocytes 6%. The urine showed only an occasional white blood cell. A blood culture was sterile as were several subsequent ones. The Wassermann reaction was positive. A Widal reaction as well as agglutination tests for melitensis and suipestifer were entirely negative. From the urine B. coli was cultured.

During the first 4 days in the hospital the patient's fever was remittent, attaining peaks of 104°. For the next 3 weeks it ranged between 100° and 102°; then for 2 weeks between 99° and 101°; for the final period it remained under 100°. The pulse rate varied between 100 and 120, usually being out of proportion to the temperature. His illness at first was characterized by drenching sweats. Ten days after admission a right footdrop appeared. About the same time it was noted that there was edema of the legs and back as well as ascites. He became weaker and continued to lose weight. A footdrop appeared on the left side as well as a right wristdrop. There was tenderness to pressure on the calf muscles and definite atrophy of the muscles of the hands. Early in November he began to complain of lower abdominal fullness. On November 10 the patient awakened to find that he was blind in the left eye. The cause for this was found to be an occlusion of the central retinal artery. Sensory disturbances in the hands, feet and about the right ear persisted. His blood pressure which had dropped as low as 138 mm. systolic shortly after admission began slowly to rise once more, attaining a level of 228/134 mm. on January 18, 1934. A moderate anemia developed, the hemoglobin falling to 70%. The leukocytes maintained a level of 12,000 to 13,000, rising above 14,300 only terminally. Eosinophils averaged 5% but at one time were as high as 13%.

The bizarre combination of findings—weakness, emaciation, fever, peripheral neuritis, abdominal pain, anemia with eosinophilia, the retinal vascular occlusion, the variable blood pressure—suggested the possibility of periarteritis nodosa, even though no nodes were ever discovered along the peripheral vessels. A piece of the left gastrocnemius muscle was therefore removed on November 22, 1933 for microscopic examination. The muscle was found to show scattered areas of atrophy. The veins were normal but the arteries showed a thickening of all coats associated with round cell infiltration and fibrosis. No definite thrombi were found although the lumina were quite narrowed. About the vessels there was a small amount of round-cell infiltration, mostly plasma cells with a few eosinophils. The media was not remarkably thickened but contained a few round cells. The intima showed the greatest relative thickening. A hyalin ring marked

the innermost portion of this coat. This picture was considered to be characteristic of periarteritis nodosa (Figs. 1 and 2).

In December edema became a more conspicuous feature. The patient had been receiving potassium iodid for some weeks. This was stopped and digitalis was given. By January the patient was reduced to a vegetative existence. He could move neither hand nor foot. His mental processes were dulled and he took no interest in his surroundings. Incontinence developed followed terminally by acute retention. At the end, the non-protein nitrogen, previously normal, rose to 90 mg.%. With a final fall of blood pressure on January 22, 1934, he died quietly, 4½ months after the onset of his acute illness. Autopsy permission was not obtained.

Additional laboratory studies provided nothing of importance. The urine contained traces of albumin, a few red blood cells and casts. The spinal fluid was normal on several occasions. An electrocardiogram showed no conspicuous abnormalities. The total proteins of the blood at first as low as 4.6 gm.%, rose promptly to normal levels with a higher protein intake. On admission the phenolsulphonephthalein excretion was 65% in 2 hours. On the day before death this value had fallen to 22%.

Discussion. The conspicuous abnormalities encountered in this individual were polyneuritis, disturbances of vision and hearing, hypertension with evidence from examination of the urine of renal disease, fever, tachycardia, edema, anemia with leukocytosis and eosinophilia, a positive Wassermann reaction and the systemic manifestations of a chronic wasting illness. Abdominal pain although present, was not striking.

Changes in the skin, usually of a hemorrhagic variety, have been observed in periarteritis nodosa. Lamb[1] refers to a case in which there was desquamation of the entire body typical of scarlet fever, without, however, any known preceding eruption. Howard[2] notes the incidence of urticaria and erythemata. Whether or not the eruption considered to be lichen planus was related to the primary disease in the present case, is, of course, problematical since no microscopic examination of the skin was made.

Polyneuritis is too frequently encountered to merit further attention. There has been ample discussion concerning the mechanism whereby changes in the peripheral nerves are produced. Evidence has been offered which indicates that the nerves may be affected either by local circulatory disturbances or else by the action of toxins in the presence of an intact blood supply.[3]

Fever, so conspicuous a symptom here, is almost invariably present at some stage in the evolution of periarteritis nodosa. Arkin[4] has more or less arbitrarily divided the course of the disease into four stages. During the first two of these: the degenerative and the acute inflammatory, fever is usual. When the processes of repair and granulation set in, the patient is afebrile. Tachycardia, likewise, is met with almost constantly.

In 34 cases reviewed by Lamb,[1] edema was observed in 61%. In the instance of the patient under discussion, anasarca, at first thought referable to reduced total blood proteins, persisted after these had been restored to a normal level.

It is reasonable to assume that syphilis had no etiological relationship to the patient's main illness. The early course of the disease transpired during a period of persistent antiluetic therapy. Although cases of periarteritis nodosa associated with a positive Wassermann reaction have been recorded, the incidence of such is no higher than in any other group of individuals. In a case reported by Gray,[5] the lesions of syphilis and periarteritis nodosa were exhibited side by side. The aorta as well as the small cerebral arteries showed characteristic luetic changes of considerable duration; while the arteries of the heart, liver, kidneys, adrenals, pancreas and lungs contained fresher lesions of a different sort, which were typical of periarteritis nodosa.

No organ is involved in this disease more frequently than the kidney. In 75% of 108 cases analyzed by Gruber[6] renal changes were encountered. As a consequence, therefore, abnormal urinary constituents are the rule. Keegan[7] had the opportunity to watch the progression of a vascular nephritis in a patient upon whom a nephrectomy had been performed 2 months before the illness terminated in uremia. Changes in the kidney removed at operation corresponded to an acute periarteritis nodosa, whereas those in the companion kidney at autopsy, indicated a vascular nephritis. From these observations Keegan concluded that certain instances of chronic arteriolosclerotic nephritis may be the sequelæ of an original periarteritis nodosa.

There was a mild secondary anemia with leukocytosis in the present case. In the more chronic forms of the disease anemia may become striking while a leukocyte count as high as 66,000 has been recorded (Lamb). Under ordinary circumstances the leukocytes range between 15,000 and 30,000.

Eosinophilia is encountered in less than 20% of the cases. In all likelihood the eosinophilia is a response to the destruction of the individual's tissues. Pathologically the same phenomenon is seen when there is infiltration about the diseased arteries by eosinophils. Certain cases have shown excessively high eosinophil counts up to 79% (Strong,[8] Curtis and Coffey[9]). The eosinophilia has aroused the suspicion of a parasitic etiology of periarteritis nodosa especially because of the fact that a disease caused by parasites, bearing certain resemblances to it, occurs in horses and dogs. In the human disease, however, parasites have never been identified.

Hypertension has been recorded in the majority of instances where the blood pressure was measured. Thus, the blood pressure was elevated in 5 out of 8 children with periarteritis nodosa included in the series collected by Rothstein and Welt;[10] while similar findings were encountered in 6 out of 7 of Strong's group. In our patient there were wide oscillations of the blood pressure, a phenomenon which appears to be of some diagnostic worth, for it was this observation which first suggested the diagnosis of periarteritis nodosa.

Over 4 years before, a man who at autopsy was found to have suffered from this disease died at this hospital. His clinical course had been most puzzling so that no satisfactory conclusions concerning the diagnosis were reached during life. It was a recollection of certain features of this man's illness that led to the first suspicion of the underlying disease in the present case. For this reason the history of the earlier case will be briefly reviewed.

CASE 2.—L. M., a Louisana lumberman of 56 (Unit No. 22019), was admitted to the hospital on December 1, 1928. In the spring of 1927 he had had mumps with testicular involvement. A year later he was treated for prostatitis. In August, 1928, a fever of obscure origin appeared and it was for this reason that he was finally admitted to the hospital. At that time the important physical findings were: loss of weight, slow mental responses, intention tremor of the hands with fibrillary twitchings, hyperactive reflexes and weakness of the extensors of the left foot. At first there was slight improvement although he continued to run a low grade fever. However, in January, 1929, a new group of findings appeared with nausea, vomiting and abdominal distention, increasing drowsiness, wandering delirium, increased rigidity of the peripheral vessels, rapidly progressive retinal arteriosclerosis with hemorrhagic retinitis and extensive exudates ending in almost total blindness, leukocytosis up to 26,700, anemia, and albuminuria. After developing pneumonia, he died on April 8, 1929. Blood pressure on admission was 150/85 mm. This soon dropped to 118/90 mm. but once again started to increase. Late in January it was 168/84 mm.: a month later 205/110 mm. Subsequently a level of 220/125 mm. was attained. *At autopsy*, the spleen was found to be enlarged. There were small nodules along the cerebral arteries. *Microscopically*, were encountered characteristic lesions of periarteritis nodosa involving the arteries of the heart, pancreas, brain, kidneys and muscles.

It was the similarity between the rapid progression of hypertension in the 2 cases, with initial elevation of pressure followed by a temporary decline and once again steady increase, that first called to mind the possibility of periarteritis nodosa explaining the symptoms of the recent case.

More detailed mention of ocular symptoms will be made, since they provided such a dramatic incident in the course of the disease in the patient under discussion. Visual disturbances were noted in 3 of the cases analyzed by Lamb. The first individual reported by Bennett and Levine[11] suffered progressive loss of vision which was compatible with the advanced vascular retinitis which existed. The young girl studied by Goldstein and Wexler[12] provided no clinical evidence of visual affliction. Pathologically, however, ocular arterial changes were discovered confined to the choroidal vessels. Friedenwald and Rones[13] examined the eyes from Case 2 with similar results. Here, likewise, inflammatory changes of periarteritis nodosa were limited to the ciliary and choroidal vessels while the retina showed extreme arteriolar sclerosis and albuminuric retinitis. These authors speculate as to the relation between the two types of vascular changes but conclude that final judgment must be suspended. Certain it is, nevertheless, that albuminuric

retinitis appears in the absence of periarteritic involvement of the retinal arteries. In support of the thesis that periarteritis nodosa is an allergic response to various infections, Helpern and Trubek[14] offer the instance of a man who succumbed to a gonococcal endocarditis and subacute glomerular nephritis, who in addition was found to have isolated lesions suggestive of periarteritis nodosa in the arteries of the testis and choroid. Here, again, the retinal vessels were entirely uninvolved. In Case 1 there was occlusion of a central retinal artery while the smaller retinal vessels showed only minimal constriction in caliber. No other example of thrombosis of the central retinal artery in periarteritis nodosa has been reported and only a single author, Müller,[15] has described retinal vascular changes of any sort.

Deafness in periarteritis nodosa is uncommon. Aside from Case 1, no mention of this symptom has been encountered. Druss and Maybaum[16] discovered acute periarteritic changes in arteries of the temporal bone of a patient dying of the disease. In addition, there were several patches of otosclerosis unassociated with any vascular abnormalities. Clinically there had been no gross disturbance of hearing. In our case the otitic involvement was of the nerve type. One can only surmise that the auditory nerves may be attacked in periarteritis nodosa in a similar manner to the peripheral nerves.

Admittedly periarteritis nodosa is a rare disease. The clinical files of this hospital disclosed in addition to the 2 cases already recalled, only 1 other example of the condition.

Case 3.—J. M. (Medical No. 54035) admitted to this hospital September 10, 1925, was a man of 23 upon whom an exploratory laparotomy was performed after several weeks of an illness characterized by fever, abdominal pain and eosinophilia. At operation small yellowish nodules along the gastric vessels and over the surfaces of the liver and spleen were disclosed. Microscopic examination proved the lesions to be periarteritic nodules.

It has repeatedly been suggested that the rarity of the ailment is partly attributable to the obvious difficulties in diagnosis. While this argument may have some clinical validity, it is unlikely that at autopsy the microscopic examination would fail to reveal the unmistakable characteristics of periarteritis nodosa. Nevertheless, 4 more instances of the disease were brought to light after a search through the pathologic records of over 13,000 autopsies. All 4 of these had, during life, masqueraded under the guise of cardiovascular renal disease; 2 dying in uremia, 1 of a cerebral hemorrhage, and 1 succumbing to myocardial failure. In only 2 cases had the pathologist ventured a suggestion of periarteritis nodosa, but a review of the sections with this disease in mind, left little doubt that all 4 represented this condition.

One other factor should be mentioned in relation to the infrequency of diagnosis of periarteritis nodosa, namely, that in a small

group of individuals the disease is not fatal. According to the statistics of Gruber[6] from 10 to 12% of the cases recover. This opinion is borne out by evidence offered by certain of the fatal cases, wherein old healed lesions in some of the viscera may be found in a person dying of involvement of a single organ in which the disease was progressive. For example, Arkin[4] records the instance of an individual whose death was attributable to cardiac and renal failure, while scarred areas produced by old periarteritic lesions were present in various other organs. It is conceivable that under certain circumstances all the lesions may heal so that for all practical purposes the patient is well, without the disease at the basis of his trouble ever having been recognized.

Conclusions. A fatal case of periarteritis nodosa without peripheral nodules, suspected and proved by biopsy antemortem, is recorded. The patient's illness was characterized by weakness, emaciation, fever, peripheral neuritis, abdominal pain, edema, occlusion of a central retinal artery, deafness, vacillating hypertension, tachycardia, anemia with leukocytosis and eosinophilia, and changes in the urine. The Wassermann reaction was positive. Potassium iodid failed to arrest the progressive course of the disease.

Mention is made of 6 other cases of periarteritis nodosa in the files of this hospital. One of these was diagnosed at autopsy; a second at laparotomy. The last 4 were recognized by searching through the autopsy material of the department of pathology.

The significance of some of the symptoms and signs encountered in periarteritis nodosa is appraised. Reasons are offered to indicate that the disease may not be quite as uncommon as the paucity of recognized cases would lead one to believe.

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THE MECHANISM OF DECREASE OF GASTRIC SECRETION WITH ADVANCING YEARS.

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While it has been known for a long time that gastric anacidity occurs much more frequently in old than in young people,[1] Bloomfield and Keefer,[2] in 1928, were the first to demonstrate the steady drop in acidity which takes place with advancing years. Polland and Bloomfield[3] subsequently confirmed this finding with carefully standardized histamin tests on essentially normal people. Vanzant and her colleagues,[4] analyzing a large mass of material, showed in addition that there was a difference between the two sexes, men on the whole having a more highly acid gastric juice than women. Finally the definitive studies of Polland[5] using histamin took into account not only age and sex but volume of secretion as well as acidity. The upshot of all this work is that the following points are established.

1. There is a marked fall in average gastric acidity of men with advancing years and the curve is a straight line.

2. The average gastric acidity of young women is distinctly lower than that of young men, but the fall with advancing years is very slight.

3. The average volume of secretion both of men and of women falls markedly with advancing years, and the curve is a straight line.

These phenomena could be explained theoretically in various ways. First, the average fall in acidity and volume of secretion with advancing years might be due to a gradual decline in each individual. On the other hand, it is conceivable that some people maintain their level of secretion unchanged throughout life whereas others suffer a very marked diminution; the curves based on average values could be the result of these two forces. And finally there

might be combinations of the two extremes. To settle this question it is necessary to measure the gastric secretion of the same series of people over intervals of years to find out what happens in the individual; the present observations represent a partial attempt to solve the problem along these lines. One can predict however on the basis of established data that the general defection of secretion with advancing years will not turn out to be due to a gradual fall in all people, because even in the older age periods a number of individuals are found who preserve a maximal secretion. Inasmuch as this secretion is still maximal it is clear that there can have been no drop from an earlier higher level. Detailed figures on this point may be found in Polland's paper.[5]

The rapidly increasing incidence of anacidity with advancing years also seems out of accord with gradual drop in secretion of the whole population.

Methods. Our plan was to repeat after a long interval the standard histamin test[6] on a series of individuals under as nearly identical conditions as possible. While we had many original observations, it was surprisingly difficult to arrange for the repetitions after a period of 5 or more years. Some of the subjects could not be located, others were unable or unwilling to return and still others presented themselves but declined to have the test. Consequently we have only 6 observations, but the information yielded seems of value.

All the tests were carried out by the same observer under as nearly constant conditions as possible. On both occasions the patient was in bed in the hospital overnight and conditions were as nearly basal as possible. Exactly the same dose of histamin was given.

In order to interpret the tests repeated after long intervals the error inherent in the method, that is to say, the amount of variation to be expected between tests done at brief intervals, must be known. We have many observations which show that if the examinations are made under standard conditions on normal people practically identical results are obtained after intervals of a few weeks or a few months. The following example will suffice:

E. M., a healthy physician, aged 28, was examined on November 1, 1928, and again on December 6, 1928. The tests are shown in Table 1. The results agree closely. The volume of juice is slightly greater on the first test and the acidity is slightly higher on the second test. In neither case is the variation over 10%, an experimental error which could hardly be lower with a method of this sort.

When the histamin test is repeated immediately or within a few days the second examination may yield slightly higher values both for volume and acidity.[7] The exact explanation is not clear.

Results. The results of the histamin test repeated after intervals of 5 years or more in 6 subjects are shown in the following protocols (Tables 2 to 7).

TABLE 1.—HISTAMIN TEST REPEATED AFTER INTERVAL OF A FEW WEEKS ON A NORMAL MAN.

10-minute period number.	Volume of secretion per 10-minute period (cc.).	Free HCl.	Total acid.
	November 1, 1928.		
	Histamin 0.6 mg.		
1	47	70	78
2	**48**	88	96
3	43	**98**	**106**
4	42	84	92
5	28	84	93
Total	208		
	December 6, 1928.		
	Histamin 0.6 mg.		
1	42	70	79
2	**45**	84	94
3	44	95	102
4	35	**105**	**114**
5	25	102	112
Total	191		

TABLE 2.—HISTAMIN TESTS DONE NOVEMBER 11, 1927, AND JANUARY 17, 1935. INTERVAL 7 YEARS. (Case 18. Male, aged 42—Neurosis.)

10-minute period number.	Volume of secretion per 10-minute period (cc.).		Free HCl.		Total acid.	
	Test 1.	Test 2.	Test 1.	Test 2.	Test 1.	Test 2.
			Histamin 0.8 mg.			
1	21	15.5	96	74	110	92
2	25	20.5	132	120	138	136
3	**28**	**24**	**144**	**123**	**150**	**139**
4	25	18.5	138	120	145	135
5	18	15	138	115	144	128
Total	117 cc.	93.5 cc.				

Comment. Here there was a moderate but definite drop in the total volume of secretion amounting to 20%. The highest 10-minute volumes on first and second tests were 28 cc. and 24 cc. Acidity on the second test was slightly less than on the first, but hardly more than can be accounted for by experimental variation.

CONCLUSION. Definite decrease in amount of secretion; slight (?) decrease in acidity.

TABLE 3.—HISTAMIN TESTS DONE APRIL 12, 1928, AND FEBRUARY 9, 1934. INTERVAL NEARLY 6 YEARS. (Case 44. Male, aged 20—No Disease.)

10-minute period number.	Volume of secretion per 10-minute period (cc.).		Free HCl.		Total acid.	
	Test 1.	Test 2.	Test 1.	Test 2.	Test 1.	Test 2.
			Histamin 0.5 mg.			
1	16	31	65	95	77	105
2	20	**35**	100	108	110	120
3	**26**	33	**135**	112	**145**	122
4	16	26	130	**116**	140	**126**
5	10	14	118	96	125	102
Total	88 cc.	139 cc.				

Comment. This case is of interest since the volume of secretion was definitely higher on the second test both as to total quantity in 50 minutes and as to greatest amount in a 10-minute period. The acidity on the other hand was distinctly lower.

TABLE 4.—HISTAMIN TESTS DONE MAY 14, 1928, AND SEPTEMBER 28, 1933. INTERVAL 5½ YEARS. (Case 46. Male, aged 27—No Disease.)

10-minute period number.	Volume of secretion per 10-minute period (cc.). Test 1.	Test 2.	Free HCl. Test 1.	Test 2.	Total acid. Test 1.	Test 2.
			Histamin 0.6 mg.			
1	10	15	85	116	98	131
2	**39**	36	114	134	120	144
3	32	**40**	126	**140**	136	**151**
4	29	35	**128**	136	**138**	150
5	24	24	128	138	132	150
Total	134 cc.	150 cc.				

Comment. The highest acidity attained after histamin was slightly *higher* in the second test. The difference is not definitely outside the limit of error. The total quantity of juice in 50 minutes is also slightly higher (a difference of 16%) although the highest volume for any one period was the same in the two tests (39 cc. and 40 cc.).

CONCLUSION. Very slight increase in gastric secretion (both volume and acid) on *second* test of doubtful significance.

TABLE 5.—HISTAMIN TESTS DONE OCTOBER 14, 1928, AND OCTOBER 5, 1933. INTERVAL 5 YEARS. (Case 60. Male, aged 41—No Disease.)

10-minute period number.	Volume of secretion per 10-minute period (cc.). Test 1.	Test 2.	Free HCl. Test 1.	Test 2.	Total acid. Test 1.	Test 2.
			Histamin 0.5 mg.			
1	15.5	4	42	34	55	45
2	27	7	96	96	103	108
3	**27**	**17**	105	**96**	**111**	108
4	19	14	**100**	100	107	**112**
5	8	11	88	55	98	60
Total	96.5 cc.	53 cc.				

TABLE 6.—HISTAMIN TESTS DONE JANUARY 8, 1928, AND OCTOBER 26, 1933. INTERVAL NEARLY 5 YEARS. (Case 74. Male, aged 39—Duodenal Ulcer.)

10-minut period number.	Volume of secretion per 10-minute period (cc.). Test 1.	Test 2.	Free HCl. Test 1.	Test 2.	Total acid. Test 1.	Test 2.
			Histamin 0.65 mg.			
1	83	**55**	76	108	84	115
2	**84**	**82**	122	116	130	128
3	74	74	**140**	**127**	**146**	**138**
4	55	63	128	118	134	129
5	53	48	124	106	132	118
Total	348 cc.	322 cc.				

Comment. The acidity was practically identical on the two tests, the highest values being 111 and 112. There was, however, a

marked drop in volume of secretion in the second test amounting to 46%.

CONCLUSION. Marked drop in volume of secretion without change in acidity.

Comment. This case is of special interest since the patient had the highest volume of gastric secretion we have ever encountered in many hundreds of tests. The results both as to acid and volume are practically identical on the two tests. The slightly lower figures on the second test are well within limit of error.

TABLE 7.—HISTAMIN TESTS DONE SEPTEMBER 20, 1927, AND SEPTEMBER 21, 1933. INTERVAL 6 YEARS. (Case 8. Male, aged 45—No Disease.)

10-minute period number.	Volume of secretion per 10-minute period (cc.).		Free HCl.		Total acid.	
	Test 1.	Test 2.	Test 1.	Test 2.	Test 1.	Test 2.
			Histamin 0.8 mg.			
1	17.5	14	56	42	74	54
2	24	19	84	75	90	94
3	25	**23**	88	92	96	112
4	**25.5**	22	96	**104**	106	**120**
5	23.5	19	**102**	97	**114**	116
6	18	12	88	94	100	112
Total	133.5 cc.	109 cc.				

Comment. The highest acidity after histamin in both tests was practically the same, the difference between 114 and 120 being within the limits of error. The volume of secretion in an hour is definitely less on the second test (a decrease of 18%), although the maximum output in a 10-minute period is practically the same (25.5 cc. and 23 cc.).

The striking fact revealed by these protocols is the slight differences in secretion between first and second tests. In all of our work on normal standards and comparative values for secretion in different people we have taken the highest acidity reached at any time during the test and the largest volume of secretion for any one 10-minute period as indicating the supreme secretory ability of that particular stomach under standard conditions of stimulation. These values, taken from the present series, are herewith tabulated (Table 8).

TABLE 8.—HIGHEST ACIDITY AND VOLUMES OBTAINED IN 6 CASES.

Case No.	Highest total acidity attained during			Highest 10-minute volume of secretion (cc.) in		
	Test 1.	Test 2.	Difference.	Test 1.	Test 2.	Difference.
18	150	139	−11	28	24	−4
44	145	126	−19	26	35	+9
46	138	151	+13	39	40	+1
60	111	112	+1	27	17	−10
74	146	138	−8	84	82	−2
8	114	120	+6	25.5	23	−1.5
Average	134	131	−3	38	36	−2

By these criteria no significant difference is made out between the first and second sets of tests, although there is perhaps a slight

tendency to lessening of acidity and volume. One must look elsewhere, then, for the explanation of the general fact that gastric secretion decreases with advancing years. The answer we believe lies in certain cases in which there is a very rapid deterioration of secretion and we are able to report 2 instances of this sort.

Case Abstracts. CASE 1.—R. N. (No. 162263), a 33-year-old teamster, was first seen in 1927 with the complaint of abdominal pain. Roentgen-ray showed a penetrating ulcer on the lesser curvature of the stomach. On April 19, 1927, even with the weak stimulus of an Ewald meal the free HCl was 48 and the total acid was 61. These findings were confirmed with an alcohol test meal. In June, 1927, he felt better after Sippy treatment, but Roentgen ray still showed the ulcer crater. He disappeared until November, 1934, when he returned with complaint of poor appetite and vomiting for a year. Reontgen ray no longer showed ulcer but the histamin test yielded *no free HCl.* He had used alcohol freely and the question of gastritis as a cause for the disappearance of acid was raised.

CASE 2.—J. D. (No. 187818), a 57-year-old photographer, was first seen in 1929 complaining of abdominal discomfort. Roentgen rays showed a penetrating gastric ulcer with pyloric obstruction. Histamin test on May 5, 1929, showed *free HCl* 88, *total* 98, highest volume per 10-minute period 41 cc. The ulcer was excised and a gastro-enterostomy was done. No large area of stomach was removed, the specimen being only a little over 1 cm. in diameter. It showed a benign gastric ulcer. On December 17, 1929, patient was well and a second histamin test showed *free HCl* 34 and *total* 44. He returned in September, 1933, with no stomach complaints but with intermittent claudication. Histamin test September 9, 1933, showed *free HCl* 0 and *total* 12, with maximum 10-minute volume 17 cc. The test was satisfactory and there was no regurgitation of bile into the stomach.

While these 2 patients were not really normal, they illustrate the fact that rapid deterioration of gastric secretion may actually take place.

Discussion. These observations show that there is no uniform steady decline of gastric secretion in all people with advancing years. In some the level of secretion remains essentially unchanged over long periods, in certain people there is a slight drop or even a slight increase and in still others a rapid failure of secretion leads to gastric anacidity. The results of these various influences gives the smooth curve of average deterioration. So far it has not been possible to correlate the course of events in the individual with any special clinical phenomena.

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CARCINOMA OF THE BREAST IN ONE OF HOMOLOGOUS TWIN SISTERS.

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Whether all malignancies in twins occur simultaneously in both is still a moot question. Bauer's[1] theory is that the constitutional tendency to cancer is based on the effect of predisposing genetic factors, and if this is correct, he states, then unicellular twins—that is, individuals of identical constitution, for they have grown from the same impregnated ovum—must both suffer from tumor or cancer, with great frequency.

According to McFarland and Meade,[2] since homologous twins arise from a single egg and consist of approximately equal quantities of material normally destined to produce a single individual, but which through some circumstances of early separation, produced two individuals, they closely resemble each other in every particular. These authors state there are no reported cases in which one homologous twin suffered from a tumor without its fellow being similarly affected. So that if one twin has cancer the other twin must necessarily have cancer too. Moreover, McFarland and Meade state such tumors occurring in homologous twins should be similar, symmetrical and simultaneous, and they quote a report of Burkhard's describing a case of cancer of the breast occurring in twin sisters at the same time.

Because of these statements, I consider it of interest to report a case that has been under my care during the past 2 years, where one twin sister had a cancer of the left breast, while the other had no evidence, either visible or palpable, of malignancy either in her breasts or elsewhere. This is the first case of malignancy in twins I have personally had to take care of in my practice.

McFarland and Meade state that twin cancer observations require that both twins shall have lived long enough to develop the disease and shall have lived near enough together for each to know about the other and for each to be studied in comparison with the other by the same observer.

The twins under consideration have lived together all their lives, 53 years, both are unmarried, both seemingly have a similar form and structure, act in similar manner in their daily habits. Both have for many years been under medical observation and under my care since January, 1933, a period of over 2 years. On February 11, 1935, the twin not affected by cancer was again carefully examined by me and no cancerous development discovered during a period of 2 years under my observation. McFarland states in a

personal communication that one should observe these cases for several years. More than 2 years should have shown malignant development in the second twin if it were destined to appear. A report of the other twin follows:*

Case Abstract. N. S., single, aged 51, was referred to me by the late Dr. Phil Graussman on January 20, 1933, for irradiation following a radical mastectomy for left breast malignancy, first noted in September, 1932, and operation performed the following month. The patient had always been well except for occasional colds, and an appendectomy in 1922. Her menstrual history was normal and without noticeable effect on her breasts; she had never been married. She and her sister dressed and acted alike and enjoyed the same kind of social and recreational activities.

In September, 1932, the patient noticed a lump in the upper quadrant of her left breast and went to her physician who advised immediate operation. Radical removal of the breast was carried out during the first week in October. The pathologic examination of the tumor showed it to be adenocarcinoma. Following an uneventful recovery from the operation, she was referred to me for postoperative irradiation. The twin sister examined at this time, showed no abnormalities except moderate deafness which had followed an attack of scarlet fever in childhood. This twin is somewhat stouter than the sister with cancer. Both sisters have wartlike papillomata on the neck.

The patient remained well until September, 1934, when a small recurrence at the site of the previous operation scar on the left breast was noted. A local resection of the recurrent malignant tissue was carried out and the patient referred for further Roentgen ray therapy. Because of the possibility of malignancy occurring in both twins, as suggested by McFarland and Meade, both sisters were again examined by me on February 11, 1935. They were found to be in good general condition, although both were simultaneously going through early evidences of menopause change. The patient whose breast had been removed showed no visible or palpable evidence of recurrence or extension of the malignant process and gave no symptoms of its presence anywhere in the body. The examination of the other sister gave no evidence whatsoever indicating the presence of cancer in her breasts or elsewhere.

It appears that here is a case which obviously is contradictory to the definite pronouncement by McFarland and Meade, and by Bauer, that cancer in homologous twins must necessarily be simultaneous. More than 2 years have elapsed since cancer appeared in the one sister, a sufficient time for cancer to have developed in her twin if it were to occur at all. The twins will be observed from time to time and any appearance of malignancy in the second twin will be reported.

* Since writing this paper the twins were again seen by me on May 29, 1935, and the second twin is still without signs of malignancy.

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CHOKED DISC IN SYPHILIS OF THE NERVOUS SYSTEM.

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The neurologist, confronted with the signs and symptoms of increased intracranial pressure and choked discs, must always give precedence to brain tumor as being the most likely possibility. Experience has shown convincingly that, though there are of course other causes, tumor is far and away the most common reason for increased pressure within the skull. One cannot emphasize too strongly, therefore, the necessity for giving it the weightiest consideration in determining the cause of choked disc and of increased intracranial pressure.

There are other causes of choked disc, however, and among the less frequent of these is syphilis of the nervous system. Recent experience with 5 cases of central nervous system syphilis has convinced us that choked disc may occur in the course of the disease, that it may disappear completely during the course of antisyphilitic treatment, and with it other signs of increased intracranial pressure. That syphilis of the nervous system may be present with brain tumor is well known, for among 22 meningeal fibroblastomas of the frontal lobes, Frazier and Alpers[1] found 3 with serologic evidence of central nervous system syphilis.

We attach little significance to positive serologic reactions in suspected cases of brain tumor. We agree with Frazier, who in a differentiation of frontal lobe fibroblastoma and syphilis, says, "In 3 of our cases serologic tests were positive, one with 20 cells and a colloidal gold curve of 554443210 in the spinal fluid. But in all 3 cases there were signs of increased intracranial pressure with papilledema of 2, 3.5 and 5 diopters. We realized, of course, that papilledema was not inconsistent with a diagnosis of syphilis, but the other signs of tumor were sufficiently outstanding to outweigh the positive serologic reactions. As a fact, it has been our practice to attach little importance to positive Wassermann reactions, either of the blood or of the spinal fluid, in persons thought to have tumors of the brain, *except when the signs of tumor are vague.* (Italics ours.) When there is indisputable evidence of a mass lesion, even though serologic tests are positive, an exploratory operation is indicated. In attaching little importance to positive serologic reports

we have been influenced in part by our experience of 30 odd years in the Neurosurgical Clinic of the University Hospital, during which time only 1 gumma has been exposed on the operating table."

This had always been our view, and is in fact the view we hold today. That syphilis of the nervous system may of itself cause choked disc has been abundantly demonstrated to us, however, in the following 5 cases which we have studied in the past year. Its differentiation from tumor will be considered subsequently.

Report of Cases. CASE 1.—*Severe headaches, diminution of vision, loss of hearing in left ear. Bilateral choked discs, partial left oculomotor weakness, deafness left ear. Blood and spinal fluid strongly positive. Complete recession of subjective symptoms and choked disc under antisyphilitic treatment.*

M. B. (D 1246) a colored woman, aged 32, was admitted to the Philadelphia General Hospital, January 26, 1934. She complained of pain in the shoulders and deafness in the left ear. She had been well until September, 1933, about 4 months before admission, when she contracted a severe head cold with much nasal discharge and profuse lachrymation. This cold lasted for 4 weeks, despite treatment. It was followed immediately by a severe constant frontal headache described as a deep, boring pain over the eyes. The headache was so severe that she was forced to give up her work; often it aroused her during the night. It lasted for 1 month and disappeared spontaneously. Shortly after this her right shoulder began to ache severely followed 1 month later by severe pain in the left shoulder. About a month before admission to the hospital she noticed that her vision was becoming dim and at times she saw double. Simultaneously, she began to develop deafness in the left ear. This progressed up to the time of admission. The only significant features in her past history were 3 children stillborn at term and the loss of 20 pounds in weight since the onset of her illness.

Examination was negative except for the neurologic features. When first examined, January 29, 1934, she had sluggish and unequal pupils, the left being the larger. The left palpebral fissure was slightly smaller and there was questionable impairment of downward movement of the left eyeball. There was decreased air conduction in the left ear. The right corner of the mouth drooped slightly at rest, but moved well on voluntary innervation.

When examined 5 days later the condition gave evidence of having progressed in the meantime. There was now a decided ptosis of the left eyelid, weakness of the left superior rectus, more marked deafness of the left ear and bilateral weakness of the soft palate. The tendon reflexes were slightly more active on the right side but there were no findings otherwise in the extremities.

Laboratory Studies. The blood Wassermann reaction was 4+. Spinal fluid (January 29, 1934) showed a pressure of 22 mm. of mercury, 87 lymphocytes, a trace of globulin, a 4+ Wassermann, and a gold sol. of 4544444321. A later spinal fluid (February 19, 1934) contained 35 lymphocytes.

The urine was normal in all respects. The blood sugar was 124; blood urea 14; red blood cell count 4,200,000; hemoglobin 85%; leukocyte count 5400 and 63% lymphocytes.

Bárány examination revealed no evidence of a cerebellopontile lesion and pointed to a supratentorial lesion.

Roentgen ray of the skull revealed no signs of increased intracranial pressure. The sella turcica was normal.

Eye Examinations. The eyes on admission (February 1, 1934) showed a choking of 5 diopters in each eye. Thirteen days later (February 14, 1934)

after antisyphilitic treatment had been under way, there were 2 diopters of swelling in the right eye and 4 in the left. One week later (February 21, 1934) shortly before discharge, there was no swelling in either eye.

Course. The patient was given intensive antisyphilitic treatment. She received 20 inunctions of mercury, 4 injections of bismuth intramuscularly and ascending doses of potassium iodid by mouth. She showed almost immediate subjective improvement. Her hearing increased and shortly before discharge became practically normal. The pain in the shoulders and neck disappeared. She left the hospital against advice free of her symptoms and neurologic signs.

The following case illustrates the need for surgical intervention in patients who do not respond to antisyphilitic treatment alone.

CASE 2.—*Severe frontal headaches and progressive loss of vision for 6 months. Progressive loss of hearing for 2 months. Bilateral choked disc. Roentgen ray evidence of left parasellar lesion. Arachnoiditis of optic chiasm exposed at operation. Recovery.*

J. G., a colored man, aged 44, was admitted to the Graduate Hospital, August 17, 1933, complaining of headache and failing vision. He had had severe, constant frontal headache for 6 months, and these were becoming progressively more intense. At times he had spells of complete loss of vision which lasted a few minutes. His vision had become worse in the 6 months before his admission to the hospital. Two months before entrance he developed ringing in his left ear and progressive loss of hearing on this side.

Examinations revealed cardiac enlargement with a blood pressure of 170/90 and generalized arteriosclerosis.

Neurologic examination showed anosmia on the left side, round, equal pupils reacting well to light and accommodation, papilledema of 2 diopters in each eye, a slight weakness of the left lower face, tremors of the fingers and a generalized hyperreflexia. There was some concentric contraction of the left visual field; the right was normal.

Laboratory Studies. The blood Wassermann reaction was strongly positive. The spinal fluid was under 22 mm. of mercury pressure. It contained 2 cells and a slight increase in protein and the Wassermann reaction was positive.

The blood count and blood chemistry were normal.

The urine contained a trace of albumin. There was 60% excretion of phenolsulphonephthalein in 2 hours.

Roentgen ray of the skull showed deformity of the sella turcica by stereoscopic views. The dorsum sellæ and posterior clinoid process on the left side were almost completely eroded. On the right side only a remnant of the posterior clinoid and dorsum sellæ remained. The signs pointed to a parasellar lesion on the left side.

Course. A course of antisyphilitic treatment consisting of mercury, iodids, bismuth and bismuth arsphenamin sulphonate was given without results, so that it was decided to explore the suprasellar and parasellar regions.

Operation. On September 21, 1933, Dr. F. C. Grant reflected a left frontotemporal bone flap. The left optic nerve was found to be covered by a heavy white membrane. This thickened arachnoid was found to extend across the anterior portion of the optic chiasm to involve the right optic nerve. This tissue was removed by blunt dissection and both nerves and chiasm freed. There was no evidence of tumor.

Recovery from the operation was uneventful. The headache disappeared

completely. Examination of the eyes (October 20, 1933) about 4 weeks after operation, revealed no choked disc.

Examination about 13 months after discharge (November 8, 1934) revealed no headache, or subjective symptoms of any sort. Examination showed only a slight weakness of the lower part of the right face.

Cases which do not respond to ordinary antisyphilitic remedies must be treated by more drastic means such as fever therapy. This is illustrated in the case which follows:

CASE 3.—*Oral syphilis 1 year previous to admission. Frontal headaches, diplopia, visual loss for 6 weeks. Bilateral choked disc, weakness right internal rectus, contraction of visual fields. Serologic evidence of central nervous system syphilis. Antisyphilitic treatment with marked improvement.*

R. S., a girl, aged 20, was admitted to the Graduate Hospital on September 7, 1934. About 1 year before admission, she had had some sores in her mouth and was treated by injections into her arms and buttocks. The sores cleared up promptly. Following this she was in good health until about 6 weeks ago, when she began suddenly to complain of frontal headaches. These were chiefly frontal but radiated also to the temporal, parietal and occipital regions. They were so severe that she was forced to give up work. At the same time she experienced photophobia, diplopia and marked disturbances of vision. She had a number of spells of numbness in the right hand during which she became momentarily speechless, but she had never suffered from spells of loss of consciousness.

Examination of her general physical being was entirely negative. Neurologic examination revealed pupils which were entirely normal in their reactions to light and accommodation. The visual fields were somewhat contracted. There was choking of 5 to 6 diopters in each eye with retinal exudates and hemorrhages. The right internal rectus was somewhat weak. Otherwise the neurologic examination was entirely negative save for absent abdominal reflexes.

Laboratory Studies. The blood Wassermann reaction was positive by the Kahn test.

The spinal fluid was under a pressure of 22 mm. of mercury. It contained 107 cells, all lymphocytes and a marked increase in protein. The Wassermann reaction was negative. The colloidal gold test was 2211333211. The spinal fluid chlorids were 656 mg.

Urinalysis was normal.

Roentgen ray of the sinuses revealed moderate clouding of both frontals, haziness of some of the right ethmoid cells, marked clouding of the left maxillary sinus, and moderate clouding of both sphenoid sinuses.

The skull Roentgen ray revealed a normal sella turcica measuring 7 by 8 mm. There was no sign of increased intracranial pressure.

Course. There were no localizing signs of brain tumor and the case was considered to be one of syphilitic meningoencephalitis. Treatment was instituted immediately. She was given mercury inunctions daily together with 10 grains of sodium iodid daily. Her headache improved greatly after a week's treatment. Since her eyes showed no improvement it was decided to treat her more intensively. She was given injections of typhoid vaccine every other day. She had as a result of these treatments 10 severe febrile reactions, her temperature rising to between 103° and 105° F. On the days when she did not receive treatment she was given a mercury inunction. In addition she received iodobismitol (2 cc. intramuscularly) every 3 or 4 days, and 30 grains of sodium iodid by mouth daily.

Under this treatment her headache disappeared entirely and her vision improved markedly. She was discharged from the hospital in good condi-

tion. She still had slight weakness of the right internal rectus muscle but no diplopia. The visual acuity in the right eye was 6/15 and in the left eye 6/9. The choked disc had receded from 5 to 6 diopters to 1.5 diopters and the visual fields were definitely fuller. Subjectively she felt in very good condition.

CASE 4.—*Memory impairment 8 or 9 months. Headache, diminution of vision, diplopia, transitory blindness for 3 months. Convulsive seizures 4 weeks. Bilateral choked disc, diminution of hearing in left ear, weakness left lower face, tremors left side, impairment of memory. Tertiary lesions on skin. Strongly positive blood and spinal fluid serology. Subjective improvement with antisyphilitic treatment.*

B. B. (29928) a colored woman, aged 47, entered the University Hospital on October 3, 1934, on the Neurosurgical Service of Dr. C. H. Frazier. She had been transferred from the Pennsylvania Hospital where she was under the care of Dr. Thomas McCrae. She had had frequent spells of loss of memory for 8 or 9 months, during which time she had noted increasing difficulty in adjustment to her environment. For 3 months, she had noticed diminution of vision, diplopia, visual hallucinations and periods of transitory blindness. She could give no further information about these various symptoms. About 4 weeks before admission to the hospital, she fell and struck her head on the floor. She was unconscious for several hours but was able to return to work in a few days. After this she was forced to remain out of work from time to time because of illness. For 4 weeks she had suffered from seizures in which she suddenly developed coarse tremor of both hands, followed quickly by sudden twitching and falling, without loss of consciousness. She had had several seizures of this sort, each one lasting about 10 minutes. She gave a history of receiving injections in her buttocks and arm. She had had 6 illegitimate children, all of whom were born dead at term. She used alcohol freely.

Examination revealed a clover form lesion on her forehead and a deformity and ulceration of the left leg. These were considered to be tertiary lesions of syphilis by the dermatologic consultant. She had in addition a severe scar involving the soft palate and tonsillar fossæ, which might very well have been due to old syphilitic lesions. The liver was enlarged.

Neurologic examination was quite variable. When first seen in the Pennsylvania Hospital, she was very much clouded, and had severe headache. Several days later in the University Hospital, she had much less headache and was much less confused. She was still disoriented and her memory was very poor. The pupils were regular, and reacted well to light and accommodation. She had incomplete loss of hearing in the left ear, a suggestive left central facial weakness, coarse tremor of the tongue, slight tremor of the left arm, and absent abdominal reflexes. At times the facial weakness was much more evident than at others. The mental responses varied widely from time to time. On some occasions there seemed to be evidence of weakness of the right hand and arm; on others it was absent. Visual field studies revealed a bitemporal hemianopsia. There was 5 diopters of swelling in each eye. There were no other significant neurologic findings.

Laboratory Studies. The blood Wassermann reaction was strongly positive. The spinal fluid was under a pressure of 190 mm. of water. It contained 85 lymphocytes and 85 mg. of protein. The Wassermann reaction was strongly positive. The colloidal gold was 0012344410. The urine was negative. Roentgen ray of the skull revealed a sella turcica which measured 14 by 8 mm. There was a suggestion of atrophy of the dorsum sellæ. The findings were suggestive of increased intracranial pressure.

Course. During the patient's stay in the hospital of 28 days, she received 20 grains of potassium iodid 3 times daily, and 8 injections of mercury succinimid (gr. $\frac{1}{4}$) intramuscularly. She improved a great deal mentally.

She became quite oriented and clear, and was able to work about the ward. The headache disappeared completely. The choking receded to 2 diopters in the left eye.

The following case illustrates a gratifying response to intensive treatment with bismuth in the presence of long-continued choked disc without loss of visual acuity.

CASE 5.—*Headache, photophobia, mental confusion and later euphoria. Increasing choked disc to 6 diopters despite antisyphilitic treatment. Disappearance of choked disc under intensive antisyphilitic therapy.*

T. P. (30310), a colored woman, aged 40, entered the University Hospital under the care of Dr. C. H. Frazier, November 28, 1934. She was transferred from the Pennsylvania Hospital where she was under the care of Dr. A. G. Fewell. In the spring of 1934, she had been troubled with sore and painful eyes, photophobia and lachrymation. This subsided and in September, 1934, she developed a generalized headache, gradual loss of vision, and increasing pain in her eyes, for which she was admitted to the Pennsylvania Hospital. The headache became more severe and the eye symptoms persisted. She became more drowsy, confused and stuporous in the hospital. She developed nausea and vomiting in addition to her other symptoms. Examination in the Pennsylvania Hospital on November 4, 1934, revealed choked disc of 3 diopters. She had a slight right central facial weakness, decreased power in the right hand grip, and astereognosis of the right hand. The blood Wassermann reaction was strongly positive. The spinal fluid examination revealed 36 cells, chiefly lymphocytes, a negative Wassermann reaction and a colloidal gold curve of 0012321000. Antisyphilitic treatment was instituted and carried out for about 4 weeks but despite this the choked disc increased to 6 diopters.

Under antisyphilitic treatment from November 2, to November 28, in the Pennsylvania Hospital, the mental confusion and stupor gradually cleared until the patient became quite clear mentally. The headache disappeared completely and the iritis which she had on admission to the hospital became much better with daily installations of homatropin. Repeated neurologic examinations revealed only unequal, irregular pupils, the right larger than the left. The right pupil reacted very sluggishly to light; the left was extremely irregular and stiff to light. Despite the remarkable improvement in the headache and in her mental state, the choked disc increased and the visual acuity became less under antisyphilitic treatment. She was transferred, therefore, to a Neurosurgical Service because, while it was felt that her condition was due to syphilitic meningitis, the increasing choked disc and the decreasing visual acuity made it advisable to keep her under observation on a surgical service where steps could be taken to save her eyesight if necessary.

Upon transfer she was quite clear mentally; she had no headache nor photophobia. Her only neurologic signs were large, irregular, fixed pupils. The blood Wassermann reaction was moderately positive. She had 5 diopters of choking in each eye and a beginning bitemporal hemianopsia. The vision was 6/20 in each eye.

Treatment. As noted previously, she received weekly injections of both bismuth and mercury in addition to iodids by mouth for 4 weeks. Despite this her choked disc continued to progress and the vision became worse.

She was then placed on 4 injections of soluble bismuth each week together with 25 to 50 grains of potassium iodid 3 times daily. She continued on this treatment for 2 weeks. In 2 days her vision increased from 6/20 in each eye to 6/6 in the right eye and 6/12 in the left eye. The choking decreased from 5 to 4 diopters in 6 days. In 8 days it had decreased to 3 diopters in

each eye. In 13 days after this intensive treatment was started, the eye-grounds showed no choking. There was only a blurring of the nasal side of the discs. Three weeks after discharge the optic discs showed no swelling whatever.

Analysis of Symptoms and Signs. *Symptoms.* In all 5 cases severe frontal headache was a constant feature. It was a severe, constant, non-throbbing ache, often radiating to the temporal or even as in 1 case, to the occipital area. On the whole, however, it was closely confined to the frontal area. The severity of the headache simulated closely that usually encountered in brain tumor. Of all the symptoms it was by far the most disabling.

Just as constant was dimness of vision which was also present in all 5 instances. Usually it manifested itself early in the disease; almost as early as the headache, for example. Once present, it appeared to progress rapidly, so that at the time of admission to the hospital it usually constituted a serious symptom. Despite its prominence and seriousness in the clinical picture, it was not often associated with a very severe loss of visual acuity.

Progressive loss of hearing in one ear was present in 3 of the 5 cases. It was a distracting but not a serious symptom. In 1 instance it loomed so large in the patient's mind that suspicion was centered on the cerebellopontile angle as the seat of the disease.

These were the three most prominent symptoms. Diplopia was an occasional complaint. Convulsions were strikingly absent except in Case 4 where it is questionable whether true convulsive seizures were ever present. The attacks referred to in the history appeared to be rather in the nature of a severe, coarse, generalized tremor. Photophobia was present in a few instances.

Signs. The most constant sign was choked disc. This was as high as 5 diopters in 4 cases and 2 diopters in the fifth. There was nothing to differentiate the process from the type of swelling of the optic nerve head seen in increased intracranial pressure due to tumor. The retina in none of the cases revealed any evidence of inflammation, and in no case was there any sign of a neuroretinitis of the syphilitic type. There was the usual appearance of swelling and protrusion of the optic nerve head with later evidences of organization.

A recent analysis of 50 cases of acute syphilitic meningitis by Drake[2] reveals choked disc in 16. The swelling varied from 2 to 5 diopters. It was bilateral in 14 and unilateral in 2 cases.

Deafness was found in 2 instances. It was a prominent subjective complaint in 3 cases.

Incomplete oculomotor palsies as seen in a unilateral ptosis with partial inferior rectus weakness in 1 case, or an incomplete internal rectus weakness in another were occasionally disclosed. A complete external ophthalmoplegia either unilateral or bilateral was never found among our 5 cases.

Despite the undoubted serologic evidence of central nervous system syphilis, the pupils were surprisingly normal in all instances. The Argyll Robertson pupil was completely lacking in all instances; indeed not even evidences of a syphilitic pupil could be disclosed.

The visual fields were normal in 2 cases. In 2 patients a bitemporal hemianopsia was present; and in the fifth case, the visual fields were generally contracted.

In 3 cases there was a slight central facial weakness, but without signs of weakness in the limbs. Tremors of the limbs, involving either one limb or several members, was found in a few cases. In 2 cases there was severe mental confusion and disorientation.

Blood and Spinal Fluid Findings. The blood Wassermann test was positive in 4 cases. It was strongly positive in 2 cases and recorded merely as positive in 2 others. The fifth case was negative.

The spinal fluid cell count was high in 3 cases: 85, 87 and 107. In 1 case, it was 36 and in another was only 2. In the cases with pleocytosis all the cells were lymphocytes.

The spinal fluid Wassermann reaction was positive in 4 cases and negative in 1.

The colloidal gold reaction was of the paretic type in 1 case and showed deviations from the normal in the other 4.

In 4 cases the spinal fluid pressure was high, 22 mm. Hg. In the other case it was about the border-line of high normal, 190 mm. of water.

The Problem of Diagnosis. The question of greatest importance, of course, is that of diagnosis. Given choked disc in a patient, how are we to determine that it is due to central nervous system syphilis and not to brain tumor? The first criterion of importance is the absence of localizing signs and the variability of those signs present. The absence of focal signs is not in itself important because there are all too many tumors which give no evidence of their location by focal signs. Taken with the other criteria however, this has some practical importance. Even more significant however, is the variability of those signs which are present. These seem to change from one examination to another. Patients who present one set of signs one day either do not exhibit these signs on subsequent examination or present totally different signs. So variable may these signs be that the question may arise whether the findings observed were really present.

Another factor of importance in diagnosis is the serology. The blood Wassermann test is always positive. There is nearly always an increase in the spinal fluid cell count, the cells being chiefly lymphocytes. There may, however, be no increase in cells as for example in Case 2, in which the meningeal reaction was so chronic that no cell rise was observed. The spinal fluid Wassermann test is usually positive but may be negative as in Case 3. The colloidal gold curve shows deviations from the normal. In the evaluation

TABLE 1.—ANALYSIS OF DATA.

Case.	Age (yrs.).	Symptoms.	Signs.	Choked disc.	Blood Wassermann reaction.	Spinal fluid.			
						Pressure.	Cells.	Wassermann reaction.	Gold sol.
1	32	Frontal headache Dimness of vision Deafness left ear	Prompt pupillary reaction to light Left pupil larger Ptosis left upper lid Deafness left ear Weakness soft palate Weakness left lower face	O.D. – 5 D. O.S. – 5 D	Strongly positive	22 mm. Hg	87	Strongly positive	4544444321
2	44	Frontal headache Failing vision Deafness left ear	Anosmia—left Regular pupils, reacting well Weakness left lower face Tremors of fingers Hyperreflexia	O.D. – 2 D O.S. – 2 D	Strongly positive	22 mm. Hg	2	Positive	
3	20	Frontal headaches Diplopia Dimness of vision Sensory Jacksonian fits Transitory aphasia	Regular pupils, reacting well Contracted visual fields Weakness right internal rectus	O.D. – 5–6 D O.S. – 5–6 D	Positive	22 mm. Hg	107	Negative	2211333211
4	47	Memory loss Dimness of vision Visual hallucinations Epileptiform seizures	Confusion and disorientation Regular pupils reacting well Loss of hearing in left ear Tremor of tongue and left arm Bitemporal hemianopsia	O.D. – 5 D O.S. – 5 D	Strongly positive	190 mm. H_2O	85	Strongly positive	0012344410
5	40	Sore eyes Lachrymation Headache Loss of vision Mental confusion	Unequal, irregular pupils, right larger than left Slight right central facial weakness Slight weakness right hand, disappearing under observation Bitemporal hemianopsia	O.D. – 5–6 O.S.	Positive	30 mm. Hg	36	Negative	0012321000

of the spinal fluid signs one may say that in a suspected case of syphilitic basilar meningitis, there is usually a decided cellular increase in the spinal fluid composed practically entirely of lymphocytes. In addition there is usually a positive Wassermann test and an abnormal colloidal gold curve. Even in the absence of a positive Wassermann reaction, however, there is usually enough in the spinal fluid findings, such as increase in cells and an abnormal gold curve, to confirm a suspicion of syphilis.

Still a third criterion for the diagnosis of choked disc due to syphilis is the response to treatment. In most cases antisyphilitic treatment is followed first by a rapid improvement in the subjective symptoms, notably the headache which is such a prominent feature of these cases. Ringing in the ears when present clears up quite rapidly and when there is a loss of hearing this too improves with treatment. The choked disc responds less rapidly. It may clear up entirely with treatment, or it may be quite resistive. In Case 2, despite the evidence for syphilis, operative interference was necessary in order to relieve the eye symptoms. With the removal of a chiasmal arachnoiditis the eye symptoms disappeared completely. In Case 4, despite the marked subjective improvement with antisyphilitic treatment, there was no recession of the choked disc at the time of discharge from the hospital. In the other cases, however, the choked disc disappeared completely (Cases 1 and 5) and almost completely (Case 3).

Too great emphasis cannot be placed on the necessity for careful observation of the visual acuity. It becomes too easy to attribute the choked disc to syphilis, and to lull oneself into a false sense of security in the belief that antisyphilitic treatment if continued long enough and intensively enough will result in complete disappearance of the choked disc. This is not necessarily true, for the choked disc may persist despite the most intensive treatment. It is essential during the course of treatment to test the visual acuity often—at least once each week. If there has been no response after a fair trial of treatment of 2 or 3 weeks, and the visual acuity is decreasing, steps must be taken to save the patient's eyesight. It may be necessary to perform a subtemporal decompression—but something must be done. If on the other hand, visual acuity does not decrease and the choking remains at the same level after a treatment period of 2 or 3 weeks, treatment may be continued provided the visual acuity is checked constantly. The response of the serology is of minor importance compared with the need for saving the eyesight.

Pathogenesis. Most of the clinical symptoms can be explained by a basilar meningitis, the cranial nerve palsies in particular. Other symptoms such as convulsions are not so readily explained on this basis. In a recent contribution Greenfield and Stern[3] report 7 cases of syphilitic hydrocephalus in adults, 6 of them with choked disc. The clinical syndrome resembled that observed in our cases

with severe headache, convulsions, choked disc, and cranial nerve palsies. They assert that the underlying difficulty is a basilar syphilitic meningitis which produces either a communicating (1 case) or non-communicating type of hydrocephalus (4 cases). We have no pathologic studies of our cases but it is quite probable that the lesions in our cases was of a similar nature.

Recently Moore[4] has reported a group of cases of acute syphilitic meningitis. Among 80 cases, one group of 26 corresponded closely to the type of case which we report. These cases were characterized by symptoms of "a rapidly developing hydrocephalus, *i. e.*, headache, nausea and vomiting, associated with symptoms of meningeal irritation. Neurologic examination in these cases showed only choked disc and stiffness of the neck." He looks upon this group as cases of acute syphilitic hydrocephalus associated with syphilitic infection of the meninges, in which there is disturbance of circulation of the cerebrospinal fluid by meningeal inflammation, mainly in the posterior fossa.

There is the further possibility that the choked disc is due to a local involvement of the optic nerve, the choking occurring from an interference with venous and lymph drainage from the retina as a result of the meningitis. This seems to have been the case in Case 2 of our series in which a choked disc of 2 diopters disappeared completely after the removal of thickened arachnoid over the optic chiasm and nerves.

The impression still prevails among clinicians that where there is evidence of choked disc in syphilis, there must be a gumma. The probabilities are much against gumma purely on the basis of statistics, for it is an established fact that gumma is a very uncommon brain lesion. Certainly the clinical features of our cases are not explainable by a solitary gumma, whereas they are readily explained by a syphilitic basilar meningitis. That this meningitis may assume gummatous characteristics has been demonstrated clearly by Jakob,[5] but this is not equivalent to saying that the clinical picture is due to a solitary gumma. There is one more important characteristic of syphilitic meningitis, and that is that it is usually accompanied by an encephalitic process of syphilitic origin, so that it is in reality a meningoencephalitis. Some of the clinical signs are explainable only on this basis; and the failure of some of the symptoms to respond to treatment may have a similar basis.

There is probably much to be said for the conception of the syphilitic hydrocephalus of Greenfield and Stern. Four of our cases had a markedly increased intracranial pressure while in the fifth the pressure was at the high limit of normal. A choked disc which was due to a local meningitis process around the optic nerves and chiasm would not produce increased pressure in the head.

Management of Syphilitic Choked Disc. Having established the diagnosis of choked disc due to syphilis, the most important problem

is that of management. How are such cases to be treated? How long can one continue with antisyphilitic treatment? When must one consider other means of treatment?

Throughout the management of the case the prime consideration is the preservation of the patient's eyesight. The subjective complaints such as headache, dizziness, mental confusion and deafness will clear up rather quickly under treatment. The choked disc will usually persist so that the problem of saving the eyesight becomes the most important one with which the clinician must deal. It must be emphasized that no set formula for the duration of antisyphilitic treatment can be set down. The duration of treatment must depend on the condition of the vision. If on biweekly examination it is found that the visual acuity is unchanged, treatment may be continued with safety so long as this prevails, provided of course, it was not too low to begin with. If on the other hand, it is found that despite treatment, the visual acuity fails regardless of whether the choked disc is increasing or not, antisyphilitic treatment must be abandoned in favor of more effective means of preserving the eyesight, as for example, subtemporal decompression. It cannot be too strongly emphasized that the eyesight is the important consideration.

These principles are well exemplified in the treatment of our cases. In Case 1, the response to treatment of the choked disc and the visual acuity was rapid and gratifying, so that antisyphilitic treatment was carried out for a period of 2 weeks without trouble. In Case 2, however, the response of the patient to treatment was not rapid enough, the vision seemed to be getting worse, and a craniotomy was necessary to save the patient's eyesight. That this was done effectively is shown by the gratifying result some time after operation. In Case 3, the response was likewise slow, but here fever therapy was substituted for other methods with resulting rapid response in the recession of the choked disc. In Case 4, antisyphilitic treatment was carried out over 6 weeks with frequent testing of the visual acuity. The result was a complete recession of the choked disc and preservation of vision. In Case 5, despite active antisyphilitic treatment the choked disc continued to advance. It was felt that all the symptoms and signs were due to syphilis but preparation for surgical intervention was made in view of the advancing papilledema. Despite this, in the presence of normal visual acuity, more intensive treatment was given, with most gratifying results. The treatment formula varies therefore with each individual case. It cannot be otherwise.

One further point is essential. The diagnosis of choked disc due to syphilis should be made either by the neurologist or neurosurgeon, otherwise there will be too many cases of choked disc due to brain tumor which are treated for syphilis, particularly since it is well

known that brain tumor and a positive blood and spinal fluid serology may be present in the same case.

Conclusions. 1. Five cases of choked disc in central nervous system syphilis are recorded.

2. Four responded well to antisyphilitic treatment. The fifth was operated on with complete relief.

3. The underlying lesion is probably a basilar meningitis.

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THE DETECTION OF TUBERCLE BACILLI IN THE BLOOD STREAM BY THE LOEWENSTEIN TECHNIQUE AND AN ANALYSIS OF LOEWENSTEIN'S INVESTIGATIONS.

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(From the Service of Dr. Bela Schick.)

Ever since 1930, Loewenstein*[1] has reported numerous positive blood cultures of tubercle bacilli, not only in tuberculosis but also in diversified conditions of unknown etiology, such as rheumatic fever, chronic polyarthritis, dementia præcox and multiple sclerosis (Table 1). During this time, the results of other investigators who had employed his technique have been either negative or positive beyond a doubt in a few cases only (Table 2). Saenz,[2] of the Pasteur Institute in Paris, tried the Loewenstein method for 4 years, with no improvement in the results. He finally concluded that the old procedure of subcutaneous inoculation of whole blood into guinea pigs gave him better results than Loewenstein's method. Popper,[3] of Maresch's Laboratory in Vienna, persisted in the use of the Loewenstein technique in 1600 cultures of blood from living persons, with only 8 (0.5%) undoubted positive results. Kolle and Küster[4] had only 7 (0.7%) positive cultures in a series of 953 cases. Each year many investigators have tried their hand at the work.

* Loewenstein's technique of culturing blood for tubercle bacilli consists of inoculating the sediment of citrated blood, freed of hemoglobin, on the surface of coagulated egg medium containing asparagin, glycerin and various salts. The inoculated culture tubes are completely sealed to prevent desiccation and incubated at 38° C. If no growth of tubercle bacilli is visible after 2 months' incubation, a smear of the surface of the medium is examined for microscopic evidence of tubercle bacilli (microscopic positive culture).

with similarly discouraging results, even after visiting Loewenstein's Laboratory.[5,6,7,et al.]

TABLE 1.—RESULTS OF BLOOD CULTURES IN LOEWENSTEIN'S LABORATORY AS REPORTED BY LOEWENSTEIN, HIS COWORKERS AND OTHER INVESTIGATORS.

Type of case.	Total cases.	Positive cases.	Per cent positive.	Author of report.
Pulmonary tuberculosis	140	54	39	Loewenstein.[1]
With intestinal tuberculosis	?	?	100	Loewenstein.[1]
With fever	?	?	80	Loewenstein.[1]
Laryngeal tuberculosis	47	26	55	Wessely, Loewenstein.[61]
Bone tuberculosis	67	26	39	Urgoiti.[62]
Urogenital tuberculosis	22	13	59	Lichtenstern.[67]
Skin diseases:				
Lupus erythematosis	33	19	58	Loewenstein (Kren).[63]
	48	3	6	Kissmeyer.[56]
Lupus vulgaris	31	11	35	Loewenstein (Kren).
	80	20	24	Kissmeyer.
	25	1	4	Konrad.[57]
Tuberculids	7	4	64	Loewenstein (Kren).
	17	1	6	Konrad.
Erythema induratum	40	21	52	Loewenstein (Kren).
Granuloma annulare	4	2	50	Konrad.
Erythema nodosum	14	12	86	Wallgren.[54]
	18	2	11	Kahlmeter.[64]
Polyarthritis:				
Acute	82	56	68	Reitter, Loewenstein.[59]
Chronic	80	27	34	Reitter, Loewenstein.[59]
Acute; chronic	1539	320	20	Loewenstein.
Diseases of the eye:				
Phlyctenular conjunctivitis, scleritis, iritis, uveitis, choroiditis	222	35	15	Loewenstein (Meller).[1]
Diseases of the central nervous system:				
Retrobulbar neuritis	6	4	66	Loewenstein.
Multiple sclerosis	111	47	42	Loewenstein.
Dementia præcox	359	142	39	Loewenstein.
	96	27	28	Kopeloff.[5]
Chorea	9	5	55	Loewenstein.
Miscellaneous:				
Bronchial asthma	?	9	..	Loewenstein.
Sepsis; grippe	39	9	..	Popper.[65]
Sepsis (staph., strept.)	?	3	..	Mach, Mach.[66]

The difficulty of culturing tubercle bacilli from the blood has been encountered with the cultures of blood from living persons only. In such cases, the positive cultures were rare and the primary growths so scant that usually only 1 or 2 minute colonies appeared. With the blood obtained at postmortem of those who died of tuberculosis, there has been no such difficulty, for the cultures have frequently been positive and the growths usually abundant.[8,9] Popper[9] has reported as many as 80 to 90% positive blood cultures from those who died of tuberculosis.

TABLE 2.—RESULTS OF BLOOD CULTURES BY THE LOEWENSTEIN METHOD IN LABORATORIES OTHER THAN LOEWENSTEIN'S.*

Type of case.	Total cases.	Positive results.					
		Macroscopic.		Microscopic.		Macro. and micro. not specified.	
		No.	%	No.	%	No.	%
Tuberculosis (all types except of skin and eye)	5472	60	1.1	122	2.2	96	1.7
Skin diseases (tuberculous forms, including lupus erythematosis, erythema multiforme, erythema induratum, erythema nodosum)	633	3	0.4	12	1.9	9	1.4
Polyarthritis (acute; chronic; rheumatic fever)	467	1	0.2	15	3.2	7	1.5
Diseases of the eye (phlyctenular conjunctivitis, scleritis, uveitis, choroiditis)	160	1	0.6	5	3.1		
Diseases of the central nervous system (multiple sclerosis, dementia præcox, chorea minor)	455	1	0.2	8	1.7		
Total	7187	66	0.92	162	2.2	112	1.6

*The data in Table 2 was compiled from the reports of the following investigators: Abt; Arloing, Dufourt; Beck; Benedek; Bernhardt; Bonnet, Legros; Brugnoghe, Adant; Courmont; Corper, Damerow; Deist; Dimtza, Gutscher; Domingo; Dobszay; Ederle, Kriech; Emslie; Fetzer, Schmitz; Hager; Harmjanz, Kortman; Huttig; Iibuchi; Jontofsohn; Kadisch; Kolle, Küster; Laymon; Levin; Lotze; Koch, F.; Kalbfleisch, Kalbfleisch; Mach, Mach; Manteufel (Holtgrave, Kottman); Münster-Frank; Okell; Paraf, Abaza; Penfold, Butler; Petersen, Lederman; Popoff, Rousseff; Popper, H.; Popper, Bodart, Schindler; Richter; Rodiet, Nevot, Maillefer; Shapiro; Saegler; Saenz; Saenz, Pascal, Costil, Chapoulaud; Schramek; Schreiner; Sergent, Durand, Gaspar, Marcoux; Siegel, Singer; Stadler; Strempel, Bürki; Schwabacher; Szüle. These references are either indicated in the text or are listed alphabetically in the bibliography from No. 69 to No. 107, inclusive.

In our own country, there have been relatively few reports of the results of blood cultures by the Loewenstein method. These published results have almost all been negative.[10,11,12,13] At Sea View Hospital, Loewenstein's method has been used since the end of 1930. Here, it was first used in 167 tuberculous cases, with 7 (4.2%) positive results.[14] In 1933, the author with the aid of Dr. Singer[15] continued the work, because Loewenstein's positive findings of the tubercle bacilli seemed to be in agreement with experimental, clinical and pathological experience. Experimentally, the ease with which disseminated tuberculosis occurs in susceptible animals, irrespective of the portal of entry, has been known for more than 50 years.[16,17] Clinically, the occurrence in our tuberculous patients, especially infants, of tuberculids, phlyctenules, miliary tuberculosis of lungs, spleen and other organs, and of other evi-

dences of hematogenous dissemination of tubercle bacilli, was seen so often that it was felt that the invasion of bacilli into the blood stream must occur frequently. Pathologically, patients dying of tuberculosis invariably had tubercles and tubercle bacilli in one or more organs remote from the seat of the main lesion. Therefore, positive cultures were expected from those critically ill with tuberculosis.

TABLE 3.—RESULTS OF BLOOD CULTURES BY LOEWENSTEIN METHOD IN TUBERCULOUS PERSONS AT SEA VIEW HOSPITAL. (SIEGEL, SINGER.[15])

Type of case.	No. of cases.	Specimens.	Results.		
			Negative.	Macroscopic positive.	Microscopic positive.
Adults—pulmonary, usually advanced or critical	332	759	708	2	49
Children—pulmonary, usually active and advanced	68	128	121	2	5
Umbilical blood of newborn of tuberculous mothers	13	13	11	1	1
Postmortem blood of newborn of tuberculous mothers	6	8	7	1	0
Postmortem blood of patients who died of tuberculosis	3	3	3	0	0
Total	422	911	850	6	55
Percentage of positive cases	..	..	...	1.4	13

The results of our first 5 months' work were disappointing. Of 150 cultures from 98 tuberculous persons, there were 3 (3%) macroscopic positive cultures and 10 (10%) microscopic positive cultures.* The macroscopic cultures grew on subculture and produced generalized tuberculosis on subcutaneous inoculation into guinea pigs. The microscopic positive cultures were negative to subculture and guinea-pig inoculation.

Since it was possible that we were not performing certain essential details in the method correctly, the author went to Loewenstein's Laboratory and worked under his supervision for 5 weeks. The work was then resumed at this hospital, with no changes in the procedure except for the use of water as a hemolytic agent instead of 3% acetic acid which had originally been employed. In spite of our previous experience and our work in Loewenstein's Laboratory, we were unable to improve our results. Of 663 specimens from 261 cases of all

* Macroscopic positive cultures were those in which colonies of tubercle bacilli were visible on the surface of the medium. If no growth was visible after 2 months' incubation at 38° C., a smear was made of the surface of the medium and examined under the microscope for acid-fast bacilli. If one or more clusters of acid-fast rods, resembling tubercle bacilli, were seen, the culture was called "microscopic positive." Smears which showed only a few isolated acid-fast rods were considered as negative and not included in the microscopic positive results.

forms of tuberculosis, usually advanced pulmonary tuberculosis, there were 1 (0.4%) macroscopic and 44 (16.9%) microscopic positive cultures. Only the macroscopic culture grew on subculture and produced tuberculosis after inoculation into guinea pigs. In part of this series, we investigated the effects of pneumothorax, thoracoplasty and surgery in bone tuberculosis in the production of a bacillemia. Before thoracoplasty, of 41 specimens from 29 patients, there was 1 microscopic positive culture. Of 200 blood specimens taken from these patients during and after operation, there were 16 microscopic positive cultures and 1 macroscopic culture. The macroscopic positive culture was obtained from a blood specimen taken immediately after the removal of the first 5 ribs in an adult with contralateral artificial pneumothorax. The postoperative course in all these cases was good, except in 1 case where the patient developed empyema. In pneumothorax, 21 specimens taken before the administration of air were negative, as compared with 2 microscopic positive cultures from 31 specimens obtained after 300 to 400 cc. of air had been given. In 7 cases of fusion operations for bone tuberculosis, all the preoperative and postoperative specimens were negative.

Thus far, of a total of 813 specimens from 359 tuberculous persons, we had 54 (15%) microscopic positive cultures and 4 (1.1%) macroscopic positive cultures. In spite of the few undoubted positive cultures (1.1%), we still felt that the tubercle bacilli were present in the blood stream of living tuberculous persons more frequently than we had demonstrated by the Loewenstein method. We, therefore, decided to compare Loewenstein's method with other methods.

With the aid of Mishulow,*[18] we were able to compare the Loewenstein method (in which the hemoglobin is removed) with the whole blood method (in which the citrated blood is cultured without removal of hemoglobin). The latter method has successfully been employed by various investigators[19,20,21,22] in detecting tubercle bacilli in the blood stream. Specimens of 4 to 14 cc. of blood were withdrawn from our tuberculous patients, and divided into two equal parts. One portion was mixed with sterile 0.4 cc. of 10% sodium citrate to prevent clotting, and was sent to Mishulow, who inoculated the whole blood directly, without preliminary removal of hemoglobin, on the surface of Loewenstein and of Bordet-Gengou media in 6 to 10 Petri plates. The other portion was cultured by us according to the Loewenstein method. The results of this series have already been published.[18] Briefly, there were 98 specimens of blood from 63 tuberculous patients, most of whom were critically ill with tuberculosis or had clinical evidence of tuberculous bacillemia. Of the 98 specimens, there were 3 macroscopic positive

* Of the Research Laboratory, New York City Department of Health, under the Director, Dr. William H. Park.

cultures by the whole blood method, as compared with 1 microscopic and 2 macroscopic positive cultures by the Loewenstein method. In no instance were both portions of a divided specimen positive by both methods. In 2 infants with miliary tuberculosis, repeated blood cultures finally gave positive results by both methods. In a third case, only the whole blood method was positive; while in the fourth case, a culture by the Loewenstein method was microscopically positive. The results of this small series seem to indicate that it is unnecessary to remove the hemoglobin from the blood. Others[2,20] also have shown that hemoglobin does not inhibit the growth of the tubercle bacilli.

Our search for the tubercle bacilli in the blood of tuberculous persons has not been abandoned. The use of saponin as the hemolytic agent[23] in the Loewenstein technique has been tried, with no increase in the number of our positive results. However, when large quantities of blood are available, saponin might still be of value, for it leaves a small sediment. At present, we are trying out Popper's modification of the Loewenstein technique with which Popper[3] has had encouraging results.*

An old method, which we have not yet given an adequate trial, is the inoculation of blood into guinea pigs. This method is preferred by Saenz[2] after 4 years' experience with the Loewenstein technique. Saenz injects the whole blood sediment into the subcutaneous tissue of the thigh and observes the guinea pig for more than 8 months if necessary. Ninni[24] prefers the injection of the blood sediment into the lymph nodes.

A summary (Table 3) of our experience with the Loewenstein technique shows that, of 911 specimens from 422 tuberculous persons, there were 6 (1.4%) macroscopic positive cultures and 55 (13%) microscopic positive cultures. The 6 macroscopic cultures were undoubted cultures of tubercle bacilli that grew readily on subculture and produced disseminated tuberculosis in guinea pigs. Only 1 or 2 colonies were seen in the primary cultures of 5 to 10 cc. of blood. Therefore, the number of detectable tubercle bacilli in the blood stream are few, and repeated blood cultures are necessary. Frequently repeated blood cultures are also important, because one does not know when and how the degree of tuberculous bacillemia varies. In pyogenic sepsis or malaria, there is a chill to tell the investigator when to take the blood specimen. In tuberculosis, there is no such guiding signal, and one depends on chance. When the clinical effects of a shower of bacilli into the blood stream, such as fresh tuberculids, are seen, it is often too late

* Popper allows the blood specimen to remain at 38° C. in a fluid nutrient medium of asparagin, di-sodium phosphate, mono-potassium phosphate, magnesium phosphate, sodium citrate, glycerin and saponin. At the end of 10 to 14 days this is centrifuged and the sediment is inoculated on the surface of Loewenstein medium. The cultures are sealed and kept in the incubator at 38° C. for 2 months.

for a culture, for most of the bacilli disappear quickly from the blood stream.[6,19]

The 55 (13%) microscopic positive results did not grow on subculture nor did they produce evidence of tuberculosis in guinea pigs. The significance of the microscopic positive cultures has not yet been determined. Until more is known about them, we shall regard them as doubtful positive results. It is obvious that the total percentage of positive results can be markedly increased by combining the microscopic and macroscopic positive results under the one heading, *positive cultures*, such as Loewenstein has done.

Our 6 macroscopic positive cultures were from various types of cases. In 1 instance, 2 minute colonies were grown from the blood of the umbilical cord. In this case, the placenta had a tuberculous area, 2 cm. in diameter. The mother died of tuberculosis 18 hours after the delivery. The newborn was a 7-month premature who died within 3 hours, with no clinical evidence of tuberculosis. The necropsy findings in the newborn were negative except for atelectatic areas in the lungs. A culture of its heart blood gave an abundant growth of tubercle bacilli in all of the culture tubes.

There were 4 other macroscopic positive cultures in our series. Two were from adults with advanced pulmonary tuberculosis. In 1 of these cases the blood specimen was taken immediately after a first-stage thoracoplasty operation in which the first 5 ribs were removed. The postoperative course was uneventful. The patient also received pneumothorax on the contralateral side. In the other case the patient was critically ill with pulmonary and intestinal tuberculosis. In 2 instances, the macroscopic positive cultures were from infants, 9 and 10 months respectively, with pulmonary and generalized miliary tuberculosis. Additional blood specimens from these 2 infants were also positive by the whole blood method, as already mentioned.

In 12 other instances, smooth, glistening, chromogenic colonies of acid-fast bacilli grew which proved to be non-pathogenic. These bacilli grew on nutrient agar at 38° C. in a few days and on Loewenstein medium at room temperature. They were saprophytic contaminants which almost all investigators who have used the Lowenstein technique have encountered. They have also been found in Loewenstein's Laboratory.[25] According to Loewenstein, they "cannot be differentiated by their shape and staining characteristics from true tubercle bacilli." They indicate the importance of subculture and virulence tests, especially of colonies obtained in non-tuberculous conditions.

Discussion. The problem of tuberculous bacillemia is an old one, and its history is important in the evaluation of Loewenstein's results. Even before Koch's discovery of the tubercle bacillus, Villemin,[16] in 1868, had shown that the causative agent of tuberculosis was in the blood stream, by producing tuberculous lesions in

a rabbit subcutaneously inoculated with blood from a tuberculous person. After the discovery of the tubercle bacillus, one of the first problems to stimulate research was the detection of the bacilli in the blood. The first to report successful results was Weichselbaum,[26] in 1884, with his report of tubercle bacilli in the smears of the postmortem blood clots of 3 cases with acute miliary tuberculosis. To these, Meisels[27] added 8 more positive results postmortem in cases of acute miliary tuberculosis. In chronic miliary tuberculosis, the smears of blood clots were negative.

In 1891, Liebman[28] aroused unusual interest in tuberculous bacillemia by reporting the presence of tubercle bacilli in smears of drops of blood of 39 out of 44 tuberculous patients after tuberculin injections. Controls from 20 normal persons were negative. However, his results were not verified by others.[29,30] Some 20 years later, several investigators reported the presence of acid-fast bacilli in the blood stream of almost all living tuberculous persons.

Rosenberger[38] (1909), using the sediment of 2 to 10 cc. of whole citrated blood, was able to report 125 positive cases from patients with tuberculosis. With the Stäubli-Schnitter[49] method Kurashige,[31] in 1911, reported 100% positive smears in 155 tuberculous cases, and about 60% positive results in 34 apparently normal persons. Suzuki and Takaki[32] followed, in 1912, with 500 positive cases out of 517 with tuberculosis. In the same year Liebermeister[33] reported many positive blood smears from tuberculous and non-tuberculous persons. His positive results in 26 out of 28 cases of pulmonary tuberculosis, 70 scrofulous patients, 37 persons with rheumatic fever, and several with erythema nodosum and angina remind one of Loewenstein's results 20 years later.

However, not all workers had such consistently good fortune. Some investigators were not successful in finding tubercle bacilli in any of their cases, even in those with tuberculosis.[29,34] Such a marked discrepancy in the results of a procedure apparently so simple as the microscopic examination of a blood smear naturally created doubt as to the reliability of the method. It was soon seen that there were many sources of error. A scratch on the slide, shreds of fibrin and débris, hemin crystals, crystals of fuchsin and incompletely decolorized smears were only a few of the things which might simulate the appearance of the tubercle bacillus. It was also soon discovered that not all acid-fast bacilli are tubercle bacilli. Rabinowitsch[35] reported that more than 60 different acid-fast forms were found between 1882 and 1902. These were present in almost all living forms, in plants, mammals, birds, reptiles and fish. They were also found in air and water, and even in distilled water.[36,37] Brem's experience with distilled water is instructive. Following Rosenberger's[38] technique, he found acid-fast bacilli in the blood smears of such non-tuberculous conditions as malaria, typhoid and pneumonia. Searching for the explanation he eventually

found non-pathogenic acid-fast bacilli in his distilled water and in all solutions made from it.

The use of animal inoculation to verify the results of blood smears varied with the different investigators. Of 125 cases positive by smear, Rosenberger[38] reported the results of intraperitoneal guinea-pig inoculation of blood sediment in 2 instances only. Both of these were said to be positive. Liebermeister,[33] in 1908, trying guinea-pig inoculation of whole blood from 50 tuberculous persons, found death from "inoculation tuberculosis" in 40% of the cases. No description of the lesions in the positive guinea pigs was given. Since these results were lower than the 100% he had obtained by blood smear, he concluded that the inoculation of guinea pigs was not sensitive enough. Suzuki and Takaki[32] claimed that animal inoculation proved their smear findings, which were positive in 510 cases. Like Liebermeister,[33] they had no controls nor did they describe the lesions in the positive inoculated animals. Where investigators described the findings in their guinea pigs, it was apparent that their diagnosis of inoculation tuberculosis was often doubtful. In most such instances[39,40,41] the workers depended on Ziehl-Neelsen smears of the blood and tissue of the guinea pig when there were no macroscopic or even microscopic tuberculous lesions 6 to 8 weeks after inoculation. Kennerknecht[41] also relied on temperature changes in her inoculated animals after subcutaneous injection of 0.5 cc. of O.T. This tuberculin test was done about 14 days after intraperitoneal inoculation of 2 cc. of the blood sample. With such criteria of inoculation tuberculosis and no controls, one does not wonder that the blood of many or of all the tuberculous and non-tuberculous cases were said to be positive. Where the animal inoculation was well controlled and the lesions in the inoculated animals were undoubtedly tuberculous, there were no positive results in non-tuberculous persons, and few positive results in tuberculous persons. Kahn,[42] in 1913, was able to collect from the literature only 32 (6.2%) out of 512 tuberculous cases in which the results of guinea-pig inoculation could be accepted as positive.

Blood cultures for tubercle bacilli were also tried. Until 1929 the positive results were less than by guinea-pig inoculation. Of 558 tuberculous cases reported from various sources, from 1906[35] to 1929, Wilson[43] was able to collect only 6 instances (1%) in which tubercle bacilli were undoubtedly cultured from the blood of living persons. Blood cultures for tubercle bacilli were rarely positive until 1930, when Loewenstein began to report his many positive results.

Loewenstein's results are striking for the types of conditions in which he reports the tubercle bacilli in the blood stream and for the high percentage of positive results in tuberculous and non-tuberculous cases. These unusual results naturally create doubt among the many investigators who have failed to verify them (Table 2),

especially as the Loewenstein method is not difficult. In his own laboratory his technician has been able to do almost all of his cultures alone. Furthermore, his medium and method, although excellent, have not been so unusual as to warrant such striking results.

The coagulated egg, asparagin, glycerin, starch or potato sugar (Kartoffelzucker) and various salts that make up the Loewenstein medium have been used for many years in making media for the tubercle bacillus. Its glycerin was introduced by Nocard and Roux[44] in 1887. Its asparagin, as a source of nitrogen, was used in 1894 by Proskauer and Beck,[45] who also recommended the various salts later used by Loewenstein. The coagulated egg was introduced by Dorset[46] in 1902, and the glycerinated egg, by Lubenau[47] in 1907. In 1930, about 25 years later, Loewenstein[1] reported the use of all these ingredients in his Congo-red medium.

Although his medium is good, Loewenstein has not depended on it alone. In 1926, Petragnani[48] introduced his malachite-green medium of potatoes, peptone, glycerin, 4 whole eggs and 1 yolk to 150 cc. of milk. This malachite-green medium, containing asparagin instead of peptone, has been constantly used by Loewenstein with his Congo-red medium. The tubercle bacilli seem to grow well on both media. The disadvantage of the Loewenstein Congo-red medium is that it contaminates easily and liquefies, thus spoiling the culture. This occurs so readily that Loewenstein never does a blood culture without using 1 to 2 tubes of the modified Petragnani malachite-green medium. On this modified Petragnani medium, Loewenstein has had about 55% of his total macroscopic positive cultures, while about 45% have been on his Congo-red medium.

The technique of culturing tubercle bacilli was introduced more than 50 years ago (1883) by R. Koch, who first grew the tubercle bacilli from various tuberculous tissues on coagulated serum. As early as 1905, Loewenstein[68] himself reported the culture of tubercle bacilli from the heart blood of experimentally infected guinea pigs. In 1906, Rabinowitsch[35] cultured the tubercle bacilli from the blood of a patient with pulmonary tuberculosis. In 1909, Anderson[50] spread the centrifuged sediment of citrated blood on glycerin potato medium, sealed the tubes with paraffin, and observed them for 2 months before discarding them as negative.

The removal of hemoglobin from the blood goes back to 1908, when Stäubli[51] used 3% acetic acid to hemolyze the blood, centrifuged the mixture, decanted the supernatant fluid and studied the sediment. In 1930, Loewenstein[1] advised the same procedure, because he felt that hemoglobin inhibits the growth of the tubercle bacilli. In 1932, he stressed the use of distilled water instead of acetic acid. Distilled water as a hemolytic agent had been employed by Burville-Holmes[37] in 1910. In 1912, Duchinoff[40] stressed

complete removal of hemoglobin by repeated washing with distilled water, a procedure which Loewenstein strongly advocates.

In addition to the complete removal of hemoglobin, Loewenstein stresses the use of 15% by volume of sulphuric acid if contamination is suspected. The principle of using a chemical substance to kill contaminants without destroying the tubercle bacilli was successfully employed by Uhlenhuth,[52] in 1908, with antiformin. In 1909, Schnitter[49] used antiformin on the sediment of blood hemolyzed by acetic acid, according to the Stäubli method. This procedure, the Stäubli-Schnitter method, became popular in the search for tubercle bacilli in the blood. Substitutes for antiformin, such as sodium hydroxid and hydrochloric acid soon appeared. In 1924, Loewenstein advised the use of 15% by volume of sulphuric acid in culturing contaminated material, such as sputum, urine and feces. In 1930, he introduced its use in culturing blood.

Since 1930, in spite of the many positive results, Loewenstein has frequently tried to improve his method and medium. As a hemolytic agent he used acetic acid (3% to 10%) for approximately his first 4500 blood cultures, but this gave an objectionable pasty sediment. To overcome this he tried saponin (from 0.5% to 2%) instead of acetic acid. In 1011 cultures, he reported 156 positive results, but discarded the saponin as "macroscopically visible colonies did not develop on the cultures." In December, 1931, he began to use distilled water which he still employs. During the years of 1930 and 1931, he not only varied his hemolytic agents, but also tried the effects of potassium hydroxid, varying from 0.5% to 2%, and 0.5 to 1 cc. of 15% by volume of sulphuric acid.

In his media, he has frequently tried new ingredients and different proportions of the old ingredients. Petragnani's[48] medium was almost always used with asparagin instead of peptone, and with varying amount of eggs and glycerin. Potato sugar replaced potato flour. For several months serum was added and occasionally asparagus water. Loewenstein's Congo-red medium also underwent many changes. The number of eggs and the amount of glycerin were usually equal to the egg and glycerin content of the modified Petragnani medium. At times the amount of asparagin was increased. For several months tomato juice, occasionally milk and even gum arabic were added. For a while water extracts of asparagus, beans and fish were also added.

Loewenstein's investigations may be criticized from two points of view—his definition of a positive blood culture and his conception of a control. For him a culture is positive either if colonies appear which he considers typical of tubercle bacilli (macroscopic positive), or if a smear of the surface of the medium, which has no visible growth after 2 months' incubation at 38° C., shows acid-fast forms which he considers tubercle bacilli (microscopic positive).

Most of the macroscopic positive cultures shown to the author

by Loewenstein had growths of typical colonies of tubercle bacilli. The primary blood cultures grew unusually well and luxuriously, unlike the minute colony or two which appeared in the primary growths obtained by other workers. In fact, his primary macroscopic cultures usually resembled the abundant growth of subcultures. Occasionally, he called yellowish or whitish growths positive which appeared rather atypical, like contaminants, either acid-fast saprophytes or non-acid-fast organisms. However, Loewenstein seemed to have no doubt that these were typical cultures of tubercle bacilli from blood sediment. He, therefore, regarded subculture and guinea-pig inoculation as unnecessary.

Although Loewenstein has had extensive experience with the tubercle bacillus, it would still be preferable if he confirmed his macroscopic positive cultures with virulence tests, especially his cultures from the blood of non-tuberculous persons. Almost all workers who have cultured blood for tubercle bacilli have had acid-fast colonies which have proved to be saprophytic on subculture and virulence tests. Of 10 macroscopic cultures from 300 tuberculous cases, Popper had 6 saprophytic strains which he believed were contaminants. Saenz reported that 3 out of his 9 macroscopic cultures in 500 tuberculous cases were non-pathogenic "paratubercle bacilli." In 120 tuberculous cases, Corper and Damerow[10] had 2 macroscopic cultures only, both of which proved to be saprophytic bacteria. Even in Loewenstein's Laboratory, Fanjul and Gerzner[25] reported 8 macroscopic cultures of saprophytic "pseudotubercle bacilli" in 45 cases with positive blood cultures.

There were relatively few microscopic positive cultures during the author's 5 weeks' visit to Loewenstein's Laboratory. In all instances, the acid-fast forms resembled tubercle bacilli. In 1 smear, a few scattered forms were seen in one field only. The remainder of this smear and smears from 2 other culture tubes of the same blood specimen were negative. In 1 other case, several groups of acid-fast bacilli were present. Smears from two other culture tubes of the specimen were filled with non-acid-fast contaminants.

The significance of a "microscopic positive culture" is doubtful. Almost every worker has seen acid-fast material in smears of the surface of media with no macroscopic growth. Some have had microscopic positive results only; others have had an occasional macroscopic positive culture (Table 2). Almost all the subcultures and guinea-pig inoculations of the microscopic positive cultures have been negative in the hands of workers other than Loewenstein, even though distinct acid-fast rods, singly or in groups like typical tubercle bacilli from colony growths, were seen. It is conceivable that in some instances the tubercle bacilli were dead and, therefore, could not grow; that at other times only slight growth occurred, so that it could not be seen with the naked eye. It is possible that the growth of the tubercle bacilli might stop with a minute colony

hidden away along the side or bottom of the culture tube. However, it is also well known that acid-fast material might be artefacts or bacilli that are not tubercle bacilli. Loewenstein, himself, stated, in 1932, that saprophytic "acid-fast bacteria cannot be differentiated by their shape and staining characteristics from true tubercle bacilli." He even considered as erroneous the many positive results of the smears of blood sediments which Rosenberger, Liebermeister, and Kurashige had formerly used to demonstrate the presence of tubercle bacilli in the blood.

Unfortunately, Loewenstein does not separate in his publications the total number of his microscopic from his macroscopic positive cultures. In his reports, he refers to them as "positive blood cultures." In his records, he also referred to them as "positive," until February, 1932, for about his first 7000 cultures. Thereafter, he indicated which of his positive cultures were "macroscopic" or "microscopic." It was soon seen that the former comprised about 55% to 60% of his total positive results.

The total number of Loewenstein's microscopic and macroscopic positive cultures has varied considerably from time to time. At times, most of his positive cultures had distinct colonies on the surface of the medium (macroscopic positive). Such was the case when the author visited Loewenstein in May, 1933. At other times, all or almost all of his cultures had no macroscopic colonies, and his positive results were based upon microscopic examination of a smear of the surface of the medium (microscopic positive). During certain periods there were many microscopic and macroscopic positive cultures. During other periods, however, almost all of his cultures were negative, even after microscopic examination. The cause of these marked variations in results has been attributed by Loewenstein chiefly to uncontrollable variations in his media and his centrifuge. At one period he claimed that the use of saponin as a hemolytic agent was the cause of his microscopic positive results. In view of these variations in Loewenstein's unusual results, it is important to know the nature of his controls and his results in these controls.

Loewenstein claims that he has had over 7000 negative control specimens to substantiate his work; that his cultures of undiagnosed blood samples, from such controls as healthy persons and those with non-tuberculous conditions, as gonorrhea, syphilis and cancer, have been negative. The details of this statement can be learned from the reports of the following workers who have sent him undiagnosed blood specimens.

Siegl,[53] of the "Wiener Kinderklinik," used blood samples from children with active tuberculosis, inactive tuberculosis, and negative reaction to tuberculin. Each sample of blood was divided into three parts. One part was sent to Loewenstein, another to Maresch, and the third part was inoculated into guinea pigs. In the entire series of 177 specimens, there was only 1 which was positive in

the inoculated guinea pigs. This positive blood was from a child with active tuberculosis. In Maresch's laboratory there were 3 microscopic positive cultures all from the children with active tuberculosis. Loewenstein, however, reported 28 positive blood cultures. He reported positive cultures in 13.5% of the specimens from the children with active tuberculosis, 18.9% from those with inactive tuberculosis, and 23.9% from those with negative tuberculin and no clinical evidence of tuberculosis. Wallgren,[54] like Siegl, also reported that Loewenstein had positive blood cultures in 3 children with repeatedly negative intracutaneous tuberculin tests to 10 mg. O.T. One child had erythema nodosum and 2 had rheumatic fever, with no clinical evidence of tuberculosis.

In skin conditions, Loewenstein seems to have had many positive blood cultures in specimens sent undiagnosed from clinically non-tuberculous persons.[55,56,57] In Delbanco's[55] series of 15 specimens from patients with tuberculous skin conditions, there was 1 (7.2%) positive culture; in 42 specimens from patients with gonorrhea, there were 7 (16.6%) positive cultures; and in 23 specimens from those with other non-tuberculous skin conditions, there were 7 (30.4%) positive cultures. Loewenstein has had positive blood cultures in such skin conditions as neurodermatitis, eczema, acne vulgaris, folliculitis;[55] furunculosis, erythema pernio, impetigo, acne vulgaris;[56] lymphatic leukemia, mycosis fungoides, acne vulgaris.[57]

Kopeloff's experience with Loewenstein is also noteworthy. Samples of blood were first sent from 42 psychotic patients clinically free of tuberculosis, and from 12 normal doctors and nurses. Kopeloff[58] divided each specimen of blood into 4 parts, gave each part a different identification number, sent 3 to Loewenstein and cultured 1 himself according to the Loewenstein technique. In this series of 54 persons, Loewenstein reported 20 positive blood cultures, 13 macroscopic and 7 microscopic, all from the psychotic patients (dementia præcox, psychoneurosis, manic depressive and involutional melancholia). None of the specimens from the normal persons was positive. All the cultures by Kopeloff were negative. Kopeloff[5] continued with the experiment. As Loewenstein received more blood specimens, he began to report macroscopic positive cultures in the clinically normal persons as well as in the psychotic patients. To complete the experiment, Kopeloff also sent 50 specimens of blood from 25 patients with active tuberculosis. In none of these specimens from cases of active tuberculosis did Loewenstein obtain a positive blood culture. In the entire series, Loewenstein had 31 macroscopic positive cultures distributed as follows:

	No of cases.	Macroscopic positive.
Active tuberculosis	25	0
Dementia præcox	96	21
Other psychoses and neuroses	19	5
Normal persons (Healthy doctors and nurses)	54	5

The macroscopic positive results were cultures of virulent tubercle bacilli as shown by subcultures and virulence tests.[5]

In spite of these many unexpected positive results,[5,53,55, *et al.*] Loewenstein claims that 7000 negative "control" specimens substantiate his work. What he evidently means by a control is a case with a negative blood culture. Once he reports the blood positive, he claims that he has demonstrated the presence of the tubercle bacilli in the blood—no matter what the clinician thinks about the case. Under experimental conditions, in which only cases with negative blood culture are considered as controls, one should use other types of controls to prove that the positive cultures come from the blood only and not from other sources.

Loewenstein has reported many other unusual findings that make adequate controls essential. He found tubercle bacilli not only in the blood of those with dementia præcox but also in their spinal fluid. He has also reported positive cultures in the blood and spinal fluid of several children with chorea. Reitter and Loewenstein[59] have reported positive cultures from the umbilical blood of 3 newborn, whose mothers had rheumatic fever with repeatedly positive blood cultures during their pre-partum period. In these instances, the newborns were normal, with negative tuberculin to 100 mg., and no clinical evidence of tuberculosis after observation periods of 5 to 12 months. The numerous positive results in non-tuberculous skin conditions have already been mentioned.[55,56,57,*et al.*] In addition, he has had positive results in such diversified conditions as polycythemia rubra, Hodgkin's disease, bronchial asthma and sepsis.

Several workers have tried to control his work by giving Loewenstein part of the blood specimen and sending the rest to other laboratories or culturing it themselves. While Loewenstein reported many positive cultures from tuberculous, non-tuberculous and clinically healthy persons, the results in other laboratories were negative.[5,53] Mathiesen[60] had a similar experience. He sent blood specimens of 51 cases of tuberculous skin diseases to Maresch's Laboratory and to Loewenstein. In Maresch's Laboratory there were no macroscopic growths and only 7 microscopic positive cultures, negative to subculture. Loewenstein reported 13 positive blood cultures. Konrad[57] also sent half of each blood specimen from persons with skin diseases to Maresch and to Loewenstein. Again, of 134 cases, Loewenstein reported 30 positive cultures, as compared with only 4 microscopic positive results in Maresch's Laboratory.

Loewenstein's explanation for the differences between his results and those of others, has been that the work in his own laboratory is superior. He cannot, however, expect this explanation to be accepted until his many positive results, especially the microscopic positive cultures, are verified by subcultures and virulence tests, and until he has satisfactory controls.

Summary. 1. Of 911 blood specimens from 422 tuberculous persons at this hospital, there were 6 (1.4%) macroscopic positive cultures and 55 (13%) microcopic positive cultures by the Loewenstein technique. The macroscopic positive cultures were undoubted cultures of tubercle bacilli according to subculture and virulence tests. The microscopic positive cultures were not definitely proved to be cultures of tubercle bacilli, since subcultures and animal inoculation gave negative results.

2. The disparity between Loewenstein's results and those of other investigators still exists after 5 years of research.

3. Loewenstein's investigations may be criticized from two points of view: his definition of a positive blood culture and his conception of a control.

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(Titles have been omitted for sake of brevity.)

BRONCHOGENIC CARCINOMA.

AN ANALYSIS OF 54 CASES WITH A ROENTGENOLOGICAL CLASSIFICATION.

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THE marked increase in the number of cases of bronchogenic carcinoma in recent years, observed in the Department of Radiology at our Institution, stimulated this review of our material. Long regarded as a rarity,[1] primary malignancy of the lung is today recognized as a tumor which occurs relatively frequently. Whether this increased incidence represents a real or apparent increase in the actual number of cases is still a mooted question.[2] In a series of 2209 autopsies, at the University of Vienna Pathological Institute,[3] Rogers found an incidence of 2.3% of bronchial carcinoma. We have observed it in 1.2% of 1773 necropsies. Prior to 1926, only an occasional case appeared in our records. In 1933, however, 23 were recognized, and during the first 9 months of the past year 19 additional cases have appeared.

In view of the recent advances in the surgical[3,4,5] and roentgenologic treatment[6,7,8] of the disease, early diagnosis has become increasingly important, for those lesions which are still localized are more amenable to treatment; whereas advanced cases, in the main, are hopeless. With this in mind, we have reviewed the cases of bronchogenic carcinoma in our hospital since 1926 (Chart I).

In all we have made a diagnosis in 123 instances. Fifty-four cases which were regarded as proven beyond doubt have been selected for detailed study. Of these, 26 were proven by bronchos-

copy with biopsy, 20 by necropsy, 4 by biopsy of accessible metastatic foci, and 4 were initially diagnosed by the presence of malignant cells in the pleural fluid sediment.

CHART I.—INCIDENCE OF BRONCHOGENIC CARCINOMA.

Year.	Total number hospital cases.	Number of cases of primary carcinoma of lung.
1926	9,429	4
1927	9,911	4
1928	10,028	14
1929	12,150	12
1930	13,263	14
1931	13,915	17
1932	14,261	16
1933	14,976	23
1934	11,204*	19
Total	109,177	123

* To October 1, 1934.

The Roentgen ray in most cases gave the original clue, but was not regarded as positive proof,[9] even though the roentgenograms may have been classical. Cases in which the bronchoscopist reported bronchial stenosis with intact bronchial mucosa alone were also discarded as unproven.[10]

Age and Sex Incidence. (Chart II.) The data reveal 72% of cases in males; 63% of the cases occurred between the fourth and seventh decade. Our youngest patient, a boy aged 12, has been under our observation for 3 years; our oldest patient was a man, aged 73. Except for the extreme youth of our youngest case, our findings are in accordance with those of other observers.

Location of the Primary Growth. (Chart III.) The location of the neoplasm in the bronchial tree is deserving of comment. Rogers,[3] Funk,[11] and Atkin[12] state that each side is about equally involved, but our figures show that the right side is slightly more susceptible to tumor growth. In our series, 29 occurred on the right side, 22 on the left and 3 in the trachea. These figures bear out Fried's[2] assertion, that bronchogenic carcinoma is more frequently observed on the right side. Manges also confirms this finding.[13]

The main bronchi were the most common sites of the primary tumor, with the upper primary divisions next in frequency. This is a fortunate circumstance, since it is obviously much more difficult to visualize tumors bronchoscopically when located in the more remote minor bronchi. Our findings are not in agreement with Rogers,[3] who found the superior bronchi more frequently involved than the main bronchi. Manges[7] and Fried's[2] data are more in accordance with our own.

Duration of Symptoms Before Hospitalization. (Chart IV.) The symptoms before hospitalization ranged from an acute onset to a duration of 3 years or more. About 20% presented symptoms of

less than 3 months' duration before admission to the hospital, while approximately half of our cases gave a time incidence of from 3 to 12 months.

CHART II.—AGE, SEX, INCIDENCE

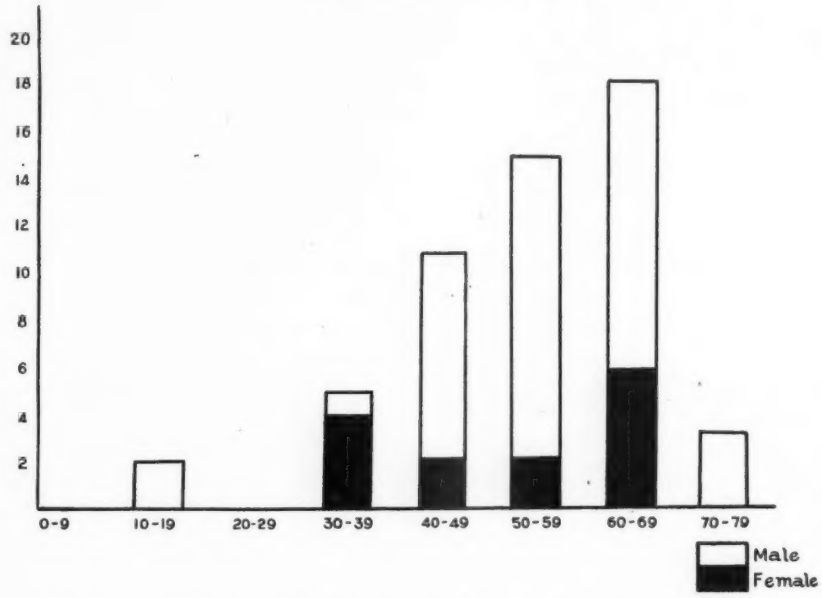

CHART III.—LOCATION OF PRIMARY GROWTH.

Right.			Left.
Main bronchus	13		12 Main bronchus
Upper bronchus	8	Trachea 2	5 Upper bronchus
Middle bronchus	2	Carina 1	
Lower bronchus	2		1 Lower bronchus
Not stated	4		4 Not stated
Total	29		22

Total, 54.

CHART IV.—DURATION OF SYMPTOMS BEFORE HOSPITALIZATION.

Time.	Number of cases.
0 to 3 mos.	11
3 to 6 mos.	13
6 mos. to 1 yr.	11
1 to 2 yrs.	3
2 to 3 yrs.	4
3 yrs. or more	3
Undetermined	9

The usual mode of onset was that of an insidious, afebrile pulmonary picture. In 16 cases (30%), the onset was atypical; of these, 5 were admitted to the hospital with a diagnosis of pneumonia

and 1 as acute cardiac decompensation. Five complained of symptoms referable to osseous metastases, 2 to symptoms of cerebral involvement, 1 to dysphagia caused by mediastinal metastases, 1 because of jaundice caused by occlusion of the common bile duct by a metastatic deposit adjacent to the head of the pancreas, and 1 presented a massive thrombosis of the venous circulation of the neck, chest, shoulders and arms.

Symptoms. A study of the symptoms, according to age groups, is presented in Chart V.

Chart V.—Symptoms.

Age groups.	Cough.	Hemoptysis.	Chest pain.	Weakness and loss of weight.	Dyspnea.	Hoarseness.
0 to 9	0	0	0	0	0	0
10 to 19	2	0	1	1	0	0
20 to 29	0	0	0	0	0	0
30 to 39	4	2	3	2	2	4
40 to 49	11	8	9	8	6	2
50 to 59	16	9	14	13	8	1
60 to 69	15	9	12	11	9	3
70 to 79	2	0	1	2	0	0
Totals	50	28	40	37	25	10

Cough, usually attributed to a bronchitis, occurred in 92% of the cases, and was the most frequent, as well as the earliest symptom. The severity of the cough varied from a slight, unproductive, irritating hack to severe harrassing paroxysms with purulent, blood-streaked expectoration. The severity of the cough was not indicative of the extent of the lesion, but in the main was dependent upon the degree of endobronchial obstruction and irritation. However, cases were noted in which the cough was minimal in the presence of a completely stenosing lesion. These, in the main, presented a diffuse luminal encroachment of the bronchus by peribronchial invasion.

Exceedingly profuse foul-smelling sputum was not encountered in this series. In no instance did we find that the usually accepted clinical picture of lung abscess overshadowed that of the bronchogenic neoplasm, although distal pulmonary suppuration was frequently found at bronchoscopy and necropsy.

Blood-streaked sputum and the occasional loss of a small amount of blood was present in 52% of our series. Frank hemorrhage was uncommon.

Chest pain was encountered in 74% of the cases. At the onset, it was mild in nature, but progressed, in some instances to the agonizing intense and persistent pain of extensive pleural involvement. We look with great suspicion upon those afebrile subjects who present chest pain, when associated with a hacking, unproductive cough.

Loss of weight and weakness were observed in 72% of the patients. Neither was appreciably present before the sixth month of the

disease. They are, as a rule, manifestations of well-advanced cases. The relative rarity of cachexia was so striking that it is deserving of special comment.

Dyspnea was also a relatively late symptom, and is probably due to extensive pulmonary involvement, mediastinal metastases or fluid. It occurred in 46% of our series. Hoarseness was present in but 18%, and may be ascribed to involvement of the recurrent laryngeal nerves by secondary deposits.

Four cases were incorrectly diagnosed; 2 were attributed to tuberculosis, and proved to be bronchogenic carcinoma at autopsy. In the third instance, the initial diagnosis of upper lobe tuberculosis was only eventually disproved after 4 bronchoscopies had been performed and a successful biopsy was obtained from the right upper bronchus. This tumor was unusually radiosensitive, and the improvement with radiotherapy was so remarkable over a period of 2 years that the diagnosis was questioned up to the time of the conclusive biopsy. The fourth case was diagnosed as a carcinoma of the thyroid with multiple metastases. At necropsy, a silent primary bronchogenic neoplasm was found.

In some instances, metastases overshadowed in significance the pulmonary symptoms, and were the first indication of the presence of malignancy. Rogers[3] states that as many as 44% of a series of 50 cases had initial symptoms caused by metastases. We have found this to be true in 18% of our cases. In 1 of these, the primary bronchial lesion was almost imperceptible, but the patient presented a well-advanced picture of intracranial metastatic malignancy. We have found no relationship between the size of the primary focus and its propensity to metastasize.

CHART VI.—METASTASES.

Autopsies, 20.

Glandular	11
Bone	9
Liver	8
Lung	8
Adrenal	6
Kidney	6
Pleura	5
Pancreas	4
Spleen	3
Skin	2
Brain	2
Thyroid	2
Heart	3
Venous thrombosis	2
Gall bladder	1
Stomach	1

In our series of 20 cases with necropsy findings, metastases (Chart VI) to the hilar, mediastinal and cervical lymph nodes were most frequently encountered with bone, lung and pleura, liver, adrenal, kidney and brain, following in the order mentioned. The mesenteric glands were also occasionally involved. Skin metastases were present in 2 of our necropsied cases (10%), and 5 of our total

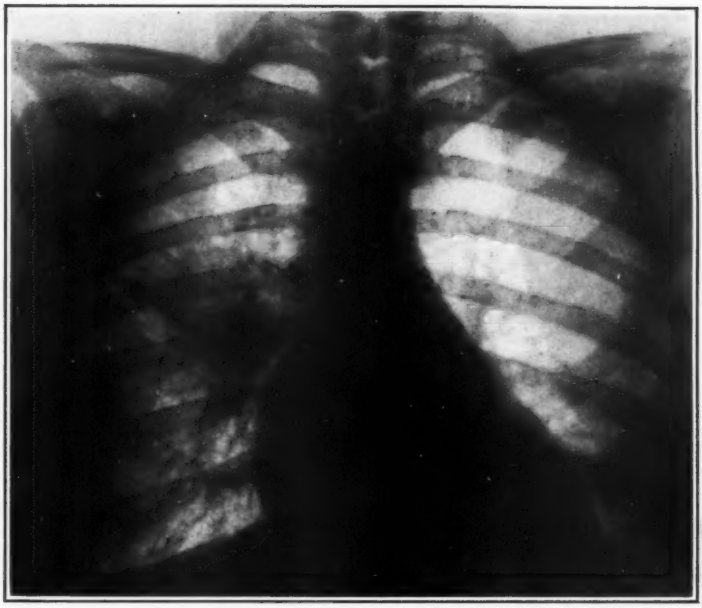

FIG. 1.—Group 1. Early. Hilar involvement, with secondary parenchymal infiltration. No elevation of the diaphragm; no fluid nor retraction of mediastinum.

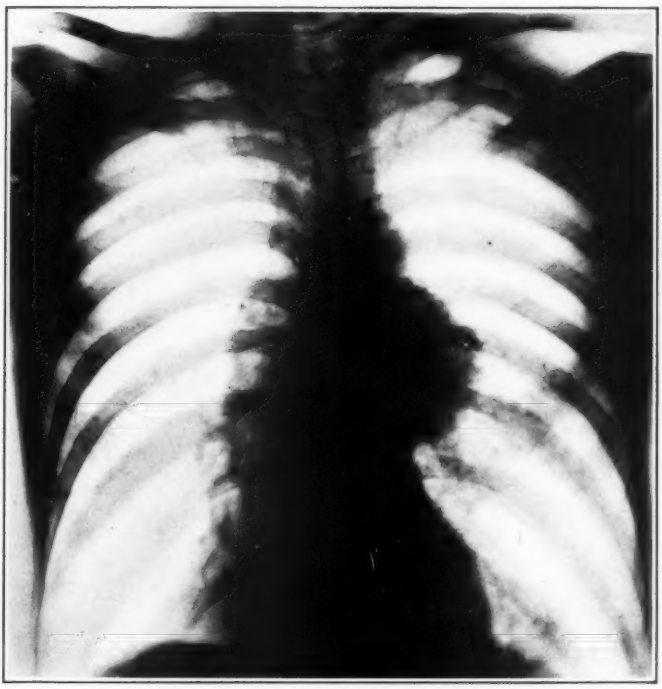

FIG. 2.—Group 1. Early. A sharply circumscribed, dense hilar opacity, with no parenchymal involvement; no diaphragmatic nor mediastinal displacement.

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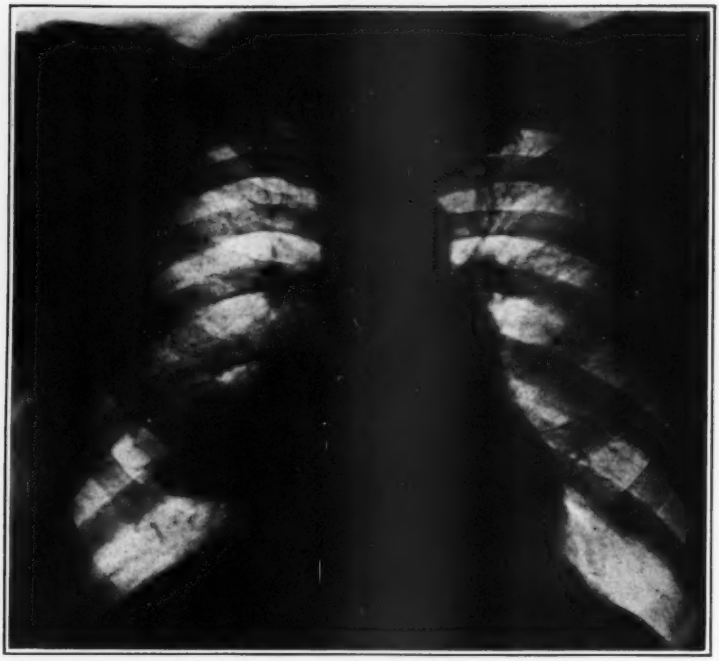

FIG. 3.—Group II. Moderately advanced. Carcinoma of right lower bronchus, with hilar and parenchymal involvement. Partial lower lobe collapse.

FIG. 3*a*.—Group II. Moderately advanced. Same as Fig. 3 following diagnostic pneumothorax.

FIG. 4.—Group II. Moderately advanced. Atelectasis resulting from a bronchogenic carcinoma of the right main bronchus in a child 12 years of age.

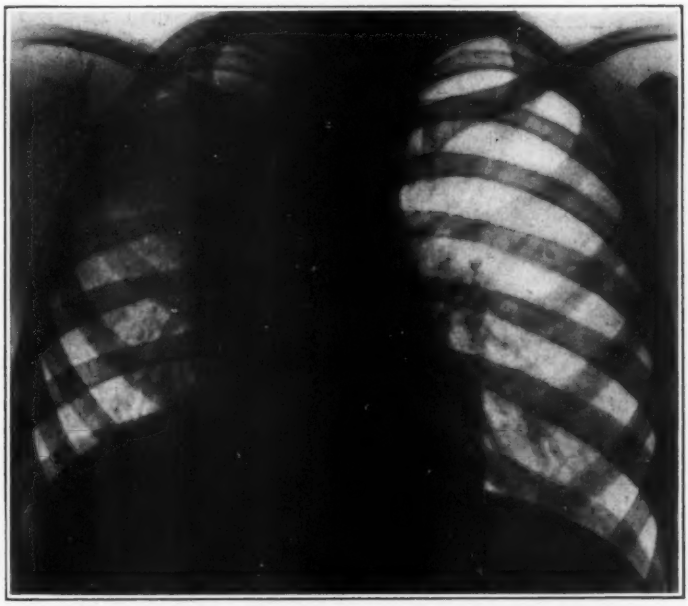

FIG. 4*a*.—Group II. Moderately advanced. Same as Fig. 4. Result 7 weeks later, after 10,800 milligram hours of radium.

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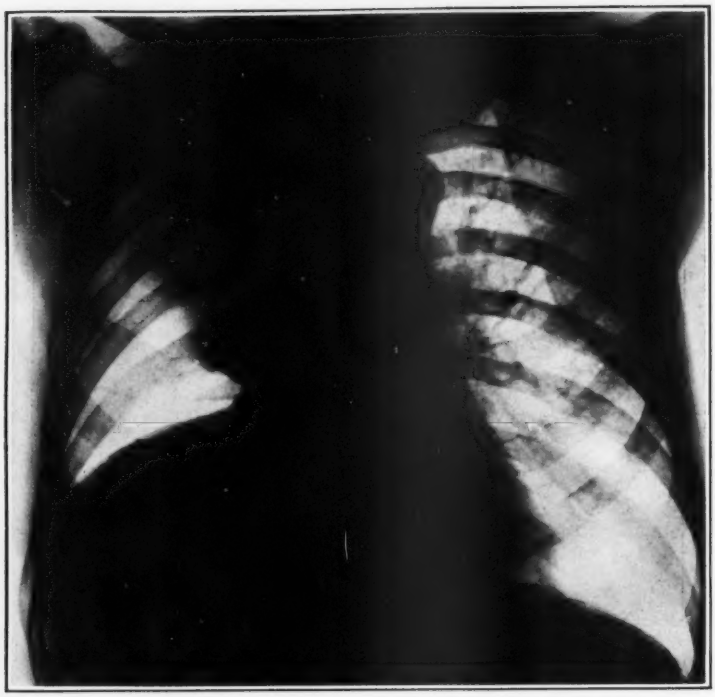

FIG. 5.—Group III. Advanced. Formerly considered alveolar type. Note marked elevation of diaphragm and diminution in size of lung field.

FIG. 6.—Group III. Advanced. Deviation of trachea toward affected side, loss of diaphragmatic shadow in overlying effusion, shift of mediastinum toward affected side, compensatory emphysema of right lung.

series. They appeared as small, hard, nodular deposits, confined mainly to the thorax and upper extremities, with normal overlying skin. The relative frequency is worthy of comment.

Once the symptoms become well established, the course, in most instances, is progressively down grade and most discouraging. Thirty-seven of our cases have died, 29 within 1 year after the diagnosis was established, 7 within 3 years and 1 after 10 years. The latter proved to be an angioendothelioma of the right main bronchus. It is questionable whether this case should be considered in the malignant group.

The radiotherapeutic results have been very discouraging, since in most of those treated, the disease was so far advanced, relief was all that could be hoped for. We were occasionally encouraged by the subsidence of cough and improvement in the radiographic picture; this was looked upon as due to diminution in the size of the neoplasm, with resultant improved drainage. We recognize, however, that an atelectatic area may at times aërate spontaneously. Two cases yielded more satisfactory results. One, a man, aged 60, was in comfort for 2 years, and the second, a boy, aged 12, is still attending school, the diagnosis having been established 3 years ago.

Our results of the treatment of osseous metastases have been more gratifying. In several instances, ossification of the rarefied neoplastic areas occurred, with complete subjective relief.

Surgery also leaves much to be desired. Those cases which present evidence of neoplastic hilar involvement are obviously too far advanced for satisfactory results. Since 72% of our series presented evidence of root infiltration, and in many of the other cases this finding was obscured by overlying fluid, one readily sees how restricted the field for surgery becomes. Those cases are best fitted for radical intervention in which the lesion is confined to a minor bronchus or the parenchyma, and which appear on the roentgenogram as an isolated, well-defined infiltrated area within the lung substance, preferably near the periphery.

Analysis of Roentgenologic Pulmonary Findings. (Chart VII.) A roentgenographic examination was made in 51 cases; in 44 of these the films were available for study. They were grouped according to the degree of pulmonary involvement from the following criteria:

CHART VII.—ANALYSIS OF ROENTGEN-RAY FINDINGS.

	Early.	Moderately advanced.	Advanced.	Total.
Number of cases	14	11	19*	44
Neoplastic hilar involvement	12	10	10	32
Hilar plus secondary bronchial infiltration	9	11	11	31
Diminution of size of affected lung field	9	11	15	35
Elevation of diaphragm	1	11	10	22
Retraction of mediastinum	0	1	10	11
Fluid	0	1	12	13
Bilateral hilar infiltration	2	8	9	19

* Findings obscured in 7 cases because of effusion.

1. Neoplastic hilar involvement—the presence of a definitely visible, unilateral circumscribed hilar shadow.

2. Hilar involvement plus invasion of the bronchial tree, extending radially into the parenchyma. This is looked upon as indicative of (*a*) venous engorgement, (*b*) bronchial infection, (*c*) peribronchial neoplastic invasion, (*d*) or the earlier degrees of bronchial stenosis. In most instances the findings are due to a combination of these factors in varying degrees.

3. Diminution in size of the affected lung field, the result of partial or complete atelectasis from bronchial obstruction.

4. Elevation of the diaphragm on the affected side, due to pulmonary atelectasis or secondary to inclusion of the phrenic nerve by mediastinal metastatic involvement.

5. Retraction of the mediastinum toward the affected side.

6. The presence or absence of fluid.

7. Bilateral hilar infiltration—in the presence of a definite unilateral lesion, increase in the size of the contralateral hilar shadow is indicative of secondary infection or metastatic involvement.

8. Bronchography by means of iodized oil.

9. Artificial pneumothorax. Bronchography and artificial pneumothorax are special radiographic procedures[14] occasionally employed and are strictly hospital measures. The former may be performed by the bronchoscopist at the time of bronchoscopic examination (active method); we, however, have obtained more satisfactory results by anesthetizing the faucial pillars and pharynx followed by direct instillation of the iodized oil under the fluoroscope (passive method). This procedure permits better visualization of that particular portion of the lung field under suspicion. Its chief value lies in the demonstration of a complete bronchial stenosis; in early cases without blockage it is of little value. Of the 13 cases so studied in our series, bronchial obstruction was demonstrated in 6 instances (46%).

The chief value of artificial pneumothorax lies in the demonstration of deposits in the parenchyma or on the pleura, and may occasionally be of help in diagnosing a lesion in a smaller bronchus. We have 1 such case in our series.

With large pleural effusions more decisive roentgenograms may occasionally be obtained immediately after thoracentesis. The microscopic examination of the sediment of the aspirated fluid is of great value. Malignant cells were demonstrated in 7 of 17 specimens examined. In 4 of these instances it was the first evidence of conclusive proof of the existence of pulmonary malignancy; in the remaining 3 it was confirmatory evidence after the diagnosis had been established by other means.

We find, from a study of these criteria, that bronchogenic carcinoma can be divided into early, moderately advanced and advanced cases. This classification is essentially an anatomico-pathologic one,

based upon the bronchial growth and its resultant pathology. It is not to be considered strictly clinical, although in the main the clinical course runs quite parallel. Fried,[2] whose classification we would follow mainly, found it difficult to classify these tumors from a gross pathologic viewpoint, but came to the conclusion that the tumors could be divided into an early and a far-advanced group.

Based upon the radiographic studies, we suggest the following classification:

1. EARLY. Hilar opacity with little or no fuzzy parenchymal infiltration. Size of lung field normal or slightly diminished. Absence of pleural fluid. Rarely, a localized small parenchymal deposit independent of the hilar shadow.

2. MODERATELY ADVANCED. As above, with the addition of definite inequality of the lung fields, elevation of the diaphragm, slight or moderate parenchymal involvement, occasionally mediastinal retraction, pleuritis and, more rarely, a small amount of pleural exudate.

3. ADVANCED. Hilar and pronounced parenchymal infiltration. Retraction of the mediastinum toward the affected side. Lung shrinkage, elevation of the diaphragm. Fluid frequently obscuring the entire radiographic picture.

GROUP I. *Early.* Fourteen (32%) of the 44 cases available for study fall into this group. Slight diminution in the size of the involved lung field was present in 9 of the cases in this group. No retraction of the mediastinum was observed. The only constant finding was the presence of a hilar opacity, with moderate secondary peribronchial infiltration (Figs. 1 and 2).

GROUP II. *Moderately Advanced.* There are 11 cases (25%) in this group. They showed a definite diminution in the size of the affected lung and elevation of the diaphragm. Retraction of the mediastinum was present in but 1 instance; fluid also was noted but once (Figs. 3, 3*a*, 4 and 4*a*).

GROUP III. *Advanced.* Nineteen (43%) of our series are in this group. Fluid was a frequent finding, in many instances completely obscuring the radiographic picture. Retraction of the mediastinum, with elevation of the diaphragm, was noted in about half of the cases. The presence of both these signs is usually indicative of a stenosing bronchial lesion, with concomitant atelectasis. Hilar opacities with marked peribronchial involvement, often sufficiently dense to obliterate lung markings, are frequently seen when not obscured by the overlying pleural fluid (Figs. 5 and 6).

Films were available for study in 17 of the 20 necropsied cases. Comparing the extent of the lesion as diagnosed by Roentgen ray with the gross pathologic findings, we find agreement in 12 cases. Two cases diagnosed as moderately advanced by Roentgen ray were found to be rather extensive; 1 case diagnosed as advanced was found to have been caused by a polyp; and 2 cases were missed

completely by Roentgen ray, 1 of which was found to have a small retrocardiac lesion in the left minor lower bronchus, and the other presented a minimal lesion in a main bronchus, the presence of which had been unsuspected.

Conclusions. Fifty-four proven cases of primary bronchogenic carcinoma are reported, with an analysis of the symptoms. We have suggested, from a radiographic standpoint, a classification into three groups—early, moderately advanced and advanced; criteria for each division have been presented.

Of 51 cases studied roentgenographically, in 23 instances a positive diagnosis was made; in 12, the diagnosis was suggested. Pleural effusion obscured the findings in 4. The diagnosis was not made in the remaining 12 cases.

Of the above cases, 31 were bronchoscoped; in 26 of these the diagnosis was conclusively established. Three cases in which the diagnosis was not made were unusual in that the lesion occurred in a subdivision of the main bronchus and was, therefore, inaccessible to the bronchoscope; in 2, no biopsy was taken.

Our statistics show that bronchoscopy is the most valuable and positive single diagnostic aid. However, since roentgenograms are readily obtained and entail no discomfort to the patient, a Roentgen ray study should be the initial diagnostic procedure. Though the film may be negative, bronchoscopy should be urged in all cases in which there is a suspicious clinical picture. It is precisely these very early lesions, not demonstrable by Roentgen ray, that may be most benefited by treatment.

The outlook for a patient with bronchogenic carcinoma is, indeed, discouraging. Until recently, the prognosis was invariably fatal. Within the past few years, more encouraging reports have appeared in the literature. It is impossible to state whether the future method of treatment will be surgical[4,6,17] or radiotherapeutic,[7,13] or a combination of both.[11] The important problem is to diagnose the case sufficiently early in order to allow surgical intervention or efficient radiotherapy. The disease is now passing into that stage of its history where the diagnosis is no longer sealed with a forlorn hope, but rather by its early detection opens the possibility of radical or palliative therapy. It is with this in mind that we reviewed our material and proposed the aforementioned classification.

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ESTIMATION OF BASAL METABOLIC RATE FROM PULSE RATE AND PULSE PRESSURE.

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Although the determination of the basal metabolic rate is now within the reach of most internists following the recent improvements in the technique and cost of the necessary apparatus, there remain a considerable number of physicians who do not find it convenient for financial or technical reasons to install such apparatus in their offices. Read[1] has attempted to calculate the basal metabolic rate from determinations of the pulse and pulse pressure. It can be appreciated that a formula for accurately predicting the basal metabolic rate in a large percentage of cases, with minimal error, would prove useful to the general practitioner.

Investigators had previously discussed the relationship between basal metabolism and pulse rate[2–4] and the increase in pulse pressure accompanying an elevated metabolic rate.[5,6] Rough estimations of the B.M.R. from the pulse rate and blood pressure had been attempted frequently. Assuming that the pulse and blood pressure changes may in many instances reflect quantitative variations in the amount of work done by the circulatory system in transporting oxygen, Read attempted to correlate these findings with the B.M.R. Three hundred determinations of the B.M.R. were made using the

Sanborn Benedict portable calorimeter; in all instances estimations of the blood pressure and pulse rate were also made. From these, Read computed coefficients of correlation between the various factors, and derived a multiple prediction formula for the estimation of the B.M.R. as follows:

$$\text{B.M.R.} = 0.683\ (\text{P.R.} + 0.9\ \text{P.P.}) - 71.5$$

where P.R. is the pulse rate and P.P. the pulse pressure. He found that in 300 cases, when pulse rate and pulse pressure were estimated under the same basal conditions as were required for the determination of the B.M.R. that the latter could be calculated with an error not more than 10% in 60% of the cases; 91% of the cases showed an error not more than 20%. He concluded from his observations that most individuals respond to variations in metabolic rate with proportionate changes in pulse rate and in pulse pressure; a few showed disproportionate changes in the one with little or no change in the other; and that a combination of the two gives a better measure of the circulatory system's response to variations in metabolic rate than either alone. In all of these calculations, he excluded patients with a systolic pressure over 160 (except young patients with marked toxic goiter) because this was attributed in most instances to pathologic changes in the cardiovascular-renal system and not to a physiologic response of the circulatory system to increased metabolism; also omitted were patients with auricular fibrillation or other cardiac arrhythmias.

Several years later, the formula was modified (on the basis of a greater number of estimations) to the following:[7]

$$\text{B.M.R.} = 0.75\ (\text{P.R.} + 0.74\ \text{P.P.}) - 72$$

At a later date, Gale and Gale,[8] studying over 1000 cases, developed a simpler prediction formula:

$$\text{B.M.R.} = \text{P.R.} + \text{P.P.} - 111.$$

which, in their hands, gave more accurate results than the Read formula.

Certain investigators have found results similar to those of Read[9–16] while calculations by others were quite at variance.[17–21] Rosenberg[13] commented on the observation that when the B.M.R. rose above 45 per cent, the calculated value (Read) tended to fall below the B.M.R. Kemeny[14] called attention to the parallelism of actual and estimated B.M.R. chiefly in cases approaching the normal. Bertheau[11] stressed the accuracy of the formula in cases of hypothyroidism; Cameron *et al.*[17] found the formula to be inaccurate in children, which has been attributed to the increased and labile pulse rate in childhood.

More recently Read and Barnett[22] have reinvestigated this problem, taking into consideration the surface area, age and sex of the

individuals. It has been shown that heat production and cardiac minute volume parallel each other rather closely. Minute volume can be roughly estimated clinically from the pulse rate and pulse pressure. It was found that the products of the pulse pressure and pulse rate were higher and the heat production lower in women than in men. Separate formulæ were then derived for the two sexes. By means of correlation tables, the following formulæ were determined.

$$\text{Men: Cals./sq. meter/hr.} = \frac{\text{P.R.} \times \text{P.P.}}{200} + 27$$

$$\text{Women: Cals./sq. meter/hr.} = \frac{3 \times \text{P.R.} \times \text{P.P.}}{700} + 24$$

From these the basal metabolic rate is then calculated in the usual manner as the percentage above or below the fixed normal standards for a given age and sex. In 100 consecutive cases (21 males and 79 females), Read and Barnett found the following:

Error not more than:

5%	10%	15%	20%	25%
59	78	94	98	100

It must be remembered that the above error signifies the difference between the observed and the calculated rates expressed in per cent deviation from normal—*i. e.*, if the observed B.M.R. were +20 and the calculated +25, the error is considered a 5%.

A series of 100 ambulatory patients (88 females and 12 males) was studied in this hospital. From these were excluded all patients with arrhythmias, hypertension, or other cardiovascular disturbances which produce alterations in the pulse rate and pulse pressure obviously not caused by changes in blood flow. Basal metabolic rates were determined in the usual way by the Sanborn Benedict apparatus, and at the same time, determinations were made of the blood pressure and average pulse rate; all determinations were made under basal conditions. From these data, the B.M.R. was calculated by three methods (Read-Barnett, Read formula 1924, and Gale and Gale). The results may be summarized as follow:

	Deviation from the observed B.M.R. not more than:					
	5%	10%	15%	20%	25%	Correlation coefficient observed: predicted.
Read-Barnett Formula						
1. U. of P. data	41	67	87	93	98	0.845
2. Read-Barnett data	59	78	94	98	100	
Read Formula (1924)						
1. U. of P. data	38	67	86	92	96	0.807
Gale and Gale Formula						
1. U. of P. data	35	54	75	84	92	0.820
2. Gale and Gale data	27			74		

Using standard statistical methods, it is found that there is no significant difference between the results obtained by the three

methods in our series of 100 patients. The correlation coefficient between pulse rate alone and B.M.R. was 0.623.

Discussion. The estimation of B.M.R. from pulse-rate and pulse-pressure data is crude, for once in 10 or 20 cases an individual prediction will be 20% too high or too low. This renders the method of little use clinically. In our series of 100 cases the various equations are not significantly different in the correlation they give with the

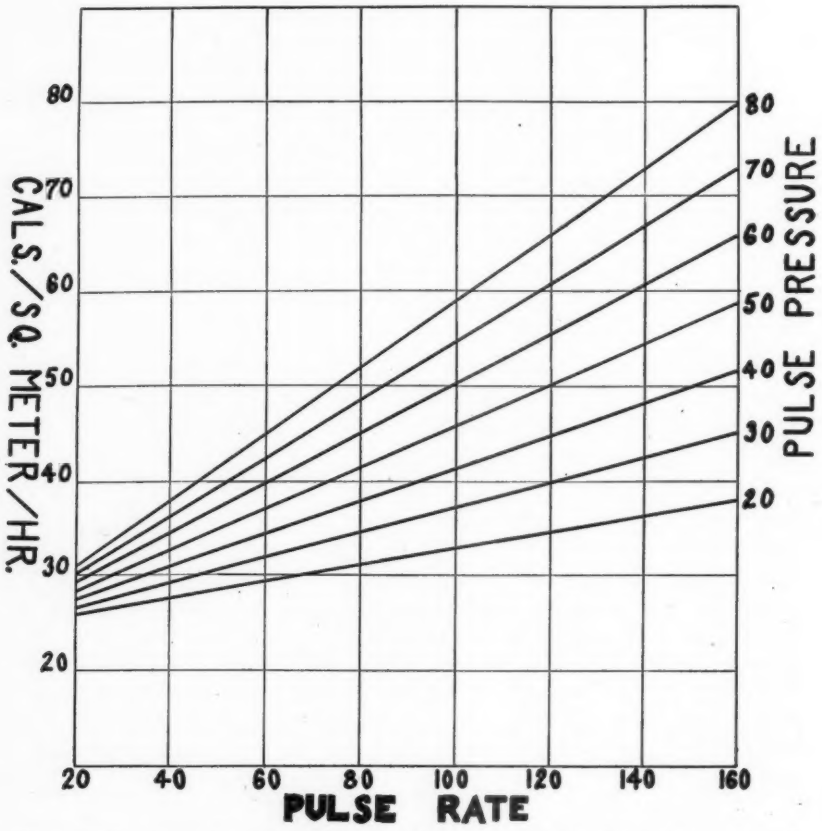

FIG. 1.—Nomogram for estimation of basal metabolic rate in females by means of Read-Barnett formula.

observed basal metabolism. The importance of disturbing factors not included in the formula is so great that attempts to refine the formula or to select the best are rather futile. If one desires to use the Read-Barnett formulæ, they can be used most conveniently in the form of a nomogram, as shown in Figure 1. The results are read directly in cals./sq. meter hr., which result is then compared with the standard accepted reading for individuals of that age and

sex, and the B.M.R. calculated as the percentage of the reading above or below the accepted standard. Gale and Gale's rule, easily remembered and requiring only mental arithmetic, gives results not significantly less good.

Conclusion. 1. The B.M.R. cannot be predicted from pulse rate and pulse pressure with significant accuracy and consistency to render the method a substitute for measurement by indirect calorimetry.

2. Gale and Gale's rule can be conveniently memorized and used, and in our hands gave resultsnot significantly less accurate in 100 cases than the more elaborate calculations of Read and Barnett.

3. If calorimetric estimation of the B.M.R. is not possible because of technical or financial difficulties, calculation of the B.M.R. from pulse pressure and pulse rate data is more accurate than attempting to guess this figure from either observation taken separately.

4. If one wishes to employ the formulæ of Read and Barnett, the use of nomograms is recommended.

We are indebted to Dr. J. Harold Austin for assistance in our statistical analysis and preparation of the nomogram.

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ANGINA PECTORIS AND HEART BLOCK,

As Symptoms of Calcareous Aortic Stenosis.

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In recent years much attention has been directed to aortic stenosis caused by calcific lesions of the semilunar valves. That the lesion is not rare is shown by various statistical studies. Thus McGinn and White[1] found aortic stenosis in 1.8% of 6800 autopsied cases of all types of disease. Yet the diagnosis was made in only ⅓ of the cases. This is a common experience. The classical physical signs are often lacking, and no distinctive symptomatology has been described.

I wish here to stress the frequency of the syndrome of angina pectoris and of conduction disturbances in patients with aortic stenosis. Not a few isolated reports of this association appear in the literature, but it has not been adequately emphasized. Years ago Allbutt[2] remarked that angina pectoris is not uncommon in patients with aortic stenosis. Mackenzie[3] believed that stenocardia in patients with aortic stenosis was due to associated changes in the heart muscle. Cabot[4] writes, "In its clinical picture aortic stenosis is peculiar not only in its proneness to occur in elderly men, but also in the frequency of precordial pain, of faintness on exertion, and of angina pectoris." McGinn and White note that 19% of their patients with aortic stenosis had angina pectoris. Margolis[5] reports 42 patients with aortic stenosis of whom 4 had angina pectoris. Tuohy and Eckman[6] point out that anginal seizures can occur in such patients whose coronary arteries are normal.

I have records of 19 private patients with aortic stenosis. Of these 4 had classical angina pectoris. The greater frequency of the anginal syndrome in a clinical rather than a pathologic series of

cases is understandable, because in many instances aortic stenosis gives rise to no symptoms and the patient dies of some intercurrent disease.

Case Abstracts. CASE 1.—A. K., a woman, aged 63, was first seen when she was 53, at which time she had no symptoms referable to her heart. She had no rheumatic history, but had had frequent sore throats. The heart was not enlarged. There was a rough systolic murmur at the aortic area, which was transmitted upward to the neck. The heart sounds were of good quality. The pulse was regular and full. The blood pressure was 90/75.

Three years later she noted for a time occasional substernal oppression on exertion. The same symptom recurred for a short period 2 years later. At 60 this symptom became more disabling and constant. Climbing stairs or walking uphill provoked a pressure sensation under the sternum which radiated to the shoulders and up the neck and compelled her to stop until the pain was relieved. Examination at this time revealed a heart considerably enlarged to the left, with a heaving apex beat in the anterior axillary line. There was a systolic thrill in the second and third interspaces, to the right of the sternum. Here a rough systolic murmur, and a musical diastolic murmur were audible. The latter was transmitted down the sternum. There was a systolic murmur at the apex.

The anginal symptoms persisted. Three years later increasing shortness of breath and a sense of oppression in the chest developed rather quickly, and the patient became bedridden. Examination revealed marked dyspnea and orthopnea, with bilateral massive hydrothorax, but no ascites nor edema. The heart findings were unchanged. On about the tenth day of this acute illness, shortly after being transported to a hospital, she suddenly experienced agonizing pain over the precordium, which radiated down the left arm, her face turned an ashen gray and there was leaden cyanosis of the lips. She was very restless, and vomited several times. She became unconscious and died within 40 minutes. It was thought that she had had an acute coronary occlusion.

The electrocardiogram taken 3 years before death showed negative *T* waves in all leads. A year later, marked left axis deviation was noted. In addition, occasional records showed marked variation in the character of the *Q–R–S* complexes. They had a supraventricular origin, but were aberrant in form, often changing from beat to beat. At one time the electrocardiogram showed transient bundle-branch block.

Autopsy (Dr. S. Jacobson, 4½ hours after death). The heart weighed 430 gm. There was marked hypertrophy of the left ventricle. All of the valves except those at the aortic orifice were normal. The cusps of the aortic valves were extremely calcified and thickened, with irregular calcified vegetations. The opening between the aortic valves was very small and rigid, measuring barely 2 mm. in diameter. The arteriosclerotic process did not involve the mouths of the coronary arteries. The coronary arteries themselves were straight and soft, with minimal sclerosis. There was no thrombus in these arteries, and there was no cardiac infarction. There was only very slight atheroma of the aorta. There were no gross scars in the myocardium, but there was some microscopic increase in the interstitial connective tissue.

CASE 2.—A man, aged 44, had had frequent attacks of tonsillitis as a boy. He had had no arthritis. At 24 he was rejected by an insurance company because of a heart lesion; 5 years later he began to be slightly short-winded, and to experience occasional sticking apical precordial pain on lifting objects. Two years prior to his first visit he commenced to experience a pinching sensation near the apex of the heart on exertion and on

excitement. Six months later attacks appeared in which the left hand would become icy cold, and this would be followed by a pressing pain along the inner aspect of the forearm. Of late this symptom had become worse. Particularly in the morning when he left the house after breakfast the left forearm became cold and he experienced a sense of pressure to the left of the sternum which compelled him to stop. He experienced similar pain on intercourse.

Examination showed a well-built man with slight cyanosis of the lips. The lungs were clear. The liver was not enlarged. Fluoroscopy revealed a huge left ventricle, the apex extending to the axilla. The other chambers were normal. The apex beat was forceful. At the aortic area there was a systolic thrill and a rough systolic murmur. A diastolic murmur was heard at the aortic area and transmitted to the apex. At the apex there was a loud systolic murmur which was transmitted to the axilla. The blood pressure was 110/65; the pulse was rather small. The electrocardiogram showed left axis deviation and sharply negative deep *T* waves in Leads I and II.

He has been under observation for 2 years following his initial examination, and the symptom of left parasternal pain on excitement or on exertion which compels him to stop his activities has persisted.

Case 3.—M. I., a man, aged 48, had had gonorrheal arthritis 25 years previously. There was no rheumatic history. He had frequent sore throats until tonsillectomy was performed 5 years prior to his first examination. He had obtained insurance at the age of 28, but 8 years later had been rated up for a murmur. Four years prior to his examination he began to experience attacks of substernal oppression which radiated to the neck and down both arms, associated with a choking sensation and difficulty in breathing. These attacks occurred on walking. They appeared more readily in cold or windy weather. The attacks gradually became more frequent and more severe, so that at the time of examination he could walk only a block before being compelled to stop. During the 8 previous months he had had a number of spontaneous attacks of similar pain at rest.

He was a well-built man of good color. The lungs were clear. The liver was not enlarged. Fluoroscopy revealed considerable enlargement of the left ventricle and of the left auricle, and slight general dilatation of the aorta. The first heart sound was of good quality. There was a musical systolic murmur at the apex. There was a faint systolic thrill and a rough systolic murmur at the aortic area. Here there was also heard a diastolic murmur which was transmitted to the apex. The blood pressure was 130/90; the pulse was small. The radial arteries were not sclerotic. The electrocardiogram showed only left-axis deviation.

Case 4.—E. K., a man, aged 37, had had several attacks of rheumatic arthritis as a young man and a heart lesion discovered at about the age of 20. He had had few symptoms referable to the heart, but recently had tired easily and had noticed some shortness of breath on walking rapidly, and had had several attacks of faintness.

He was a well-built man. The lungs were clear, the liver not enlarged. Fluoroscopy revealed moderate enlargement of the left ventricle and some dilatation of the ascending aorta. There was a systolic thrill at the aortic area, as well as a rough systolic murmur. A diastolic murmur was also heard here and transmitted along the left sternal margin. At the apex there was a systolic murmur transmitted to the axilla. The blood pressure was 120/70.

For about 1½ years following the first examination there was little change in his condition. He experienced frequent joint pains in the ankles, wrists and fingers, and occasional shooting precordial pain, worse on exertion.

He never had fever. His heart rate always ranged around 90. At this time he took 16 cc. of tincture of digitalis in 3 days, and on the fourth day felt very faint and experienced soreness in the precordium, which radiated down the left arm. Examination revealed complete heart block, with a ventricular rate of 50, an auricular rate of 100, and many extrasystoles. Four days later normal rhythm was restored.

Following this he was quite inactive and felt well for 3 months, when one night he awakened with precordial pain which radiated down the left arm and which lasted all the following day. He felt very weak. For a few days previously he had experienced fleeting pains in the joints and a slight sore throat. Examination revealed no change in the physical findings. There was normal sinus rhythm, with a heart rate of 90 to 100. No fever followed this upset, but he felt weak and the precordial pain occasionally recurred. One week later the rate suddenly dropped to 60, and the day following to 48, and the electrocardiogram again revealed complete heart block. At this time he complained of pain in the left arm. Ever since then there have been frequent spontaneous changes in the cardiac mechanism, from sinus rhythm to partial heart block to complete heart block. At rest there was the usual sinus rhythm, with a heart rate of 80, but walking caused a drop in rate to 60 with the appearance of heart block and occasional pain in the left arm. The sedimentation rate of the red blood cells at this time was 3 hours.

About 1 month after the first appearance of the heart block he began to experience precordial oppression radiating down the left arm, on walking about a block. This symptom persisted ever after, and indeed gradually became more severe. The appearance of heart block on exertion too was common.

Three years after he was first examined, and 13 months after the first appearance of heart block, he developed a fulminating lobar pneumonia involving both lower lobes. On the third day he suddenly complained of intense epigastric pain. His color became ashen, the pulse feeble, and he died after about 1 hour. No autopsy was obtained.

Case 5.—D. C., a man, aged 34, who had never had rheumatic fever or sore throats, had been told at 24 years of age that he had a valvular lesion. He had had no symptoms referable to the heart until 6 weeks previously, when he noted substernal pressure, dyspnea and orthopnea which prevented him from falling asleep. These symptoms had persisted.

Examination revealed a rather pale man, not dyspneic at rest. The lungs were clear. The liver extended 3 finger breadths below the costal margin. Fluoroscopy revealed huge enlargement of all of the chambers of the heart, particularly of the left ventricle, with some fullness of the pulmonary conus. The aorta was small. The first heart sound was of good quality, and at the apex there was a loud systolic murmur which was transmitted to the axilla. At the aortic area there was a systolic thrill, and a rough systolic murmur was audible. A diastolic murmur was heard along the left sternal border. The heart rate was 36, with frequent extrasystoles. The electrocardiogram revealed complete heart block, with ventricular extrasystoles. The blood pressure was 170/80.

The patient did well on diuretics, particularly of the mercurial type, but heart failure recurred and he finally died of that condition 1½ years after his first visit. Complete heart block had persisted during this whole period.

No autopsy obtainable.

Case 6.—M. H. (No. 374837), a woman, aged 52, had had no rheumatic episodes. For 20 years she had had intermittent swelling of the ankles. Diabetes was discovered 2½ years previously. For the past year and a half she had experienced gradually increasing dyspnea on exertion, and occa-

sional attacks of nocturnal dyspnea. Two months previously she began to have an unproductive cough, which persisted. Five days before admission to the hospital she was awakened from sleep by an attack of severe dyspnea and orthopnea, with sharp precordial pain which radiated to the back, was aggravated by cough and relieved by lying down. The pain and dyspnea lasted an entire day. She was then up and about. On the night before admission to the hospital she was again seized with intense dyspnea and precordial pain.

Physical Examination on Admission. She was profoundly dyspneic and cyanotic, perspiring profusely, with frequent cough, and looked acutely ill. There were moist râles throughout both lower lobes. The heart was slightly enlarged. The first sound was feeble, the pulmonic second sound accentuated, and there was gallop rhythm at the apex. The pulse was very weak and rapid. The blood pressure was 160/100. The liver was felt 4 finger breadths below the costal margin. The white blood cell count was normal. She did not rally. Her condition grew progressively worse; she became comatose and died on the fourth day after admission.

On the day following admission the blood pressure dropped to 94/78. The temperature ranged from 101 to 104, and finally reached 106° just before death. The urine was normal except for a trace of albumin. The Wassermann reaction was negative. The blood urea was 22 mg. per 100 cc.

The *electrocardiogram* on the day of admission showed left axis deviation, slurring of the *Q–R–S* complex and low *T* waves in all leads. Three days later the voltage of the electrocardiogram was lower, the slurring of the *Q–R–S* was more marked, and the *T* wave in Lead IV became isoelectric. The clinical diagnosis was coronary thrombosis.

Autopsy (Dr. Bernheim, 10 hours after death). The heart weighed 500 gm. There was marked dilatation, particularly of the right auricle and right ventricle. The aortic cusps were rigid, calcific and markedly thickened. The right and posterior cusps were fused. There was marked narrowing of the aortic orifice. The coronary ostia were wide open, and the coronary arteries were patent throughout. There was a mucopurulent bronchitis and tracheitis. There was marked acute passive congestion of the viscera, a small hydrothorax, and ascites.

Comments. The first 4 cases illustrate the gradual development of the anginal syndrome with the progress of the aortic narrowing. In Case 1 the evolution of the symptoms paralleling the advancing valvular lesion is particularly striking. In this case, too, the autopsy revealed essentially normal coronary arteries.

On the basis of the prevalent theory that the anginal syndrome is caused by anoxemia or ischemia of the heart muscle, the mechanism in these cases is readily understandable. The blocking of the blood flow to the myocardium takes place at the aortic orifice instead of in the coronary arteries themselves. A casual inspection of some of these valves deformed by calcified nodules reveals how extreme this obstruction can be. Moreover, it impairs the blood supply in the territories of both the right and left coronary arteries simultaneously, in contrast to the more localized area of impeded blood flow usually occurring in coronary arteriosclerosis.

In Case 4 the anginal syndrome was always more accentuated when, as a result of the appearance of heart block, the heart rate dropped to 40. Because of the narrowed aortic orifice, the heart

could not compensate for this slowed rate by increasing the stroke volume, so that relative ischemia of the heart muscle occurred. I have seen analogous phenomena in patients with very tight mitral stenosis who felt very uncomfortable, with increased dyspnea and other evidences of heart failure, when the pulse became too slow. In one woman with sinoauricular block the heart rate often ranged between 40 and 46. During such a period she was very uncomfortable, and was relieved of many of her symptoms when the rate rose to 80 or 90. I have seen a number of patients with mitral stenosis and auricular fibrillation in whom evidences of congestive failure increased when the ventricular rate as a result of digitalis administration dropped to 50 or 60, and who improved when the rate again reached the neighborhood of 80, if there was no accompanying demand for increased work of the heart.

When the aortic orifice is greatly narrowed, rapidly developing heart failure by still further retarding the blood flow through the minute opening may induce an acute myocardial ischemia analogous to that following coronary artery thrombosis and giving rise to identical symptoms. This is dramatically illustrated by the sudden death of Case 1 following a shocking attack of precordial pain, and of Case 2 shortly after the abrupt onset of intense epigastric pain in the course of lobar pneumonia. In Case 6 the complete clinical picture of coronary thrombosis was simulated by advanced heart failure in the presence of a tight aortic stenosis.

Angina pectoris has often been noted in patients with aortic insufficiency, and since all of my patients had aortic insufficiency as well as stenosis it might be asserted that it was the incompetency, rather than the narrowing of the valve that was responsible for the cardiac pain. Heart pain in patients with aortic insufficiency is of two main types. In syphilitic aortic insufficiency the true anginal syndrome is common and is caused by the encroachment of the luetic lesion on the mouths of the coronary arteries, with resultant narrowing. There is rarely, if ever, stenosis of the aortic valve. More rarely paroxysmal cardiac pain is observed in young individuals with rheumatic aortic insufficiency.[7,8] This is not a true Heberden's angina. The pain is not related to effort and is associated with marked vasomotor disturbances. Intense precordial pain which often radiates down one or both arms is accompanied by extreme throbbing of the heart and arteries, tremendous rise in blood pressure, and a rapid heart rate. The mechanism of these attacks is not clear, but it is certainly of a different nature than that of classical angina pectoris. In patients with calcareous aortic stenosis, neither of the above mechanism is called into play. It is significant that the calcific lesion does not extend up the sinuses of Valsalva to block the orifices of the coronary arteries.

Still less attention has been paid to the clinical manifestations of conduction defect in patients with aortic stenosis. Yet this associa-

tion too, while not as frequent as the anginal syndrome, is not uncommon. Its anatomic basis was established years ago by Mönckeberg, and has been well summarized by Uehlinger.[9] The calcification commonly spreads from the aortic valves to the annulus fibrosus and to the interventricular septum, often impinging upon and destroying the auriculoventricular bundle. East[10] recorded 2 cases in which the calcified masses had spread from the aortic valve down into the septum and had caused disturbances in conduction. Years ago, before the recognition of heart block, Parkes Weber,[11] described a patient with aortic stenosis and a pulse rate of 44. Allbutt[12] observed 2 similar patients, 1 with a pulse rate of 40 and the other 30. In Uehlinger's case a subacute bacterial endocarditis had been engrafted upon a calcific aortic-stenotic lesion, and the inflammatory reaction had invaded the bundle and produced heart block. A very similar case has been described by Lemierre and Rudolph.[13] Campbell and Shackle[14] observed a number of patients with aortic stenosis and bundle-branch block.

In the present series, Case 1 showed transient bundle-branch block, Case 5 had complete heart block, and Case 4 had intermittent heart block.

The etiology of the calcific lesion has given rise to much difference of opinion. The ages of our patients at the onset of the anginal syndrome were 35, 44, 42 and 56 years, respectively. The development of the lesion in early adult life militates against the view that it is caused by a degenerative process of senescence. Clawson[15] has pointed out that in these patients the degree of senile arteriosclerosis of the aorta is less than in persons of similar age without this lesion, and has inferred from this that the injury to the aortic cusps begins early in life; for the narrowed aortic orifice protects the aorta from the usual forceful impact of the blood ejected with each systole. Clawson, too, noted a history of rheumatic infection in many of his cases, and concluded that the aortic calcific lesion was the end result of an infectious process. Christian[16] holds a similar opinion. With this view I agree. The lesion seems to develop in individuals who have experienced a solitary, or even a subclinical rheumatic infection in childhood or in early life. The rheumatic process does not progress, but a gradual calcification of the injured valve takes place. Valvular deformity seems to favor more rapid development of atheroma and calcification.

Summary. The syndrome of angina pectoris is common in patients with aortic stenosis. It appears to be caused, not by disease of the coronary arteries, but by the narrowing of the aortic valvular opening itself, which impairs the blood supply to both coronary arteries simultaneously. Sudden heart failure in these patients is often followed by symptoms simulating coronary thrombosis.

Auriculoventricular conduction disturbances are also often associated with the calcific form of aortic stenosis. These are determined

by extension of the calcific process into the annulus fibrosus, or ventricular septum. At times a secondary infection of the diseased valve causes heart block by direct extension into the auriculo-ventricular bundle. Isolated aortic stenosis is probably of rheumatic origin.

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A COMPARATIVE STUDY OF THE GEOGRAPHIC DISTRIBUTION OF RHEUMATIC FEVER, SCARLET FEVER AND ACUTE GLOMERULONEPHRITIS IN NORTH AMERICA.

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Although certain epidemiologic studies on scarlet fever and rheumatic fever are available, comprehensive data on the geographic distribution of acute glomerulonephritis are lacking. This paper

presents a study of the incidence of acute glomerulonephritis in 24 hospitals in North America from 1910 through 1931. These data have been compared with the incidence of rheumatic fever in the same hospitals from 1910 through 1925. The statistics on the geographic frequency of scarlet fever compiled by Schroeder and Longacre[1] have been made available for comparative study.

Method of Obtaining Data. The method of obtaining the data for the incidence of rheumatic fever has been described in a previous paper.[2] In that study questionnaires were sent to a representative group of hospitals in North America for information as to the number of cases of rheumatic fever, number of medical admissions, and number of total admissions over a period of years. From the information thus obtained the conclusion was drawn that "the yearly admission rate for rheumatic fever in a selected series of hospitals in the United States and Canada is greater in the northern than in the southern regions of the continent."

In pursuance of limited studies on the etiology and mechanism of acute nephritis a similar questionnaire was sent to the *same* group of hospitals requesting information on the yearly incidence of acute nephritis. Adequate data were received from 24 hospitals.

It was obvious that the number of cases reported from each hospital would in part depend upon such factors as the presence or absence of pediatric or contagious services. Although no accurate correction could be made for this variable, it was found that the presence or absence of such services was uniform in the various geographical regions. In order to minimize inaccuracy, the yearly incidence of acute glomerulonephritis was always considered in terms of the yearly *medical admission rate*, rather than the *total admission rate*. By this method the recorded frequency of acute nephritis would not be influenced by the presence or absence of large obstetrical or surgical services in one hospital as compared with another.

In a number of instances the hospital statistics failed to give the medical admission rate over a number of years, although the total hospital admission rate was made available. The medical admission rate was, therefore, calculated on the basis of special information furnished by the respective hospitals. In some instances the medical admission rates obtained in this study failed to agree with the rates furnished in answer to the first questionnaire sent in 1926. In most cases the differences were negligible. In certain reports, however, the spread of the two figures was surprisingly large and the final accepted figure was determined on the basis of the known total admission rate.

It was realized that the diagnosis of acute glomerulonephritis might vary somewhat in the hospitals studied, but it was felt that the degree of error produced by the inclusion of cases of nephritis due to bichlorid of mercury poisoning, for example, would not be significant.

The statistics for the geographical distribution of scarlet fever have been compiled by Schroeder and Longacre from the United States Public Health Reports and forms a part of their accompanying paper.

Presentation of Data. The tables contain the data for rheumatic fever and scarlet fever from which the graph has been constructed. The incidence of these diseases over a period of years is shown for the four latitude areas selected. The figures for scarlet fever included in the accompanying paper are in terms of cases per 100,000 population from the years 1919 through 1931. The data for rheumatic fever and acute glomerulonephritis are derived from the *same* hos-

TABLE 1.—RHEUMATIC FEVER, ACUTE NEPHRITIS AND TOTAL ADMISSIONS TO MEDICAL WARDS IN 24 HOSPITALS IN THE UNITED STATES AND CANADA.*

	Good Samaritan, Portland, Ore.			Vancouver General, Vancouver, B. C.			Winnipeg General, Winnipeg, Man.			Royal Victoria, Montreal.		
	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.
1910	..	..	....	..	..	....	..	..	....	41	7	1363
1911	..	..	....	..	..	....	..	..	....	53	11	1475
1912	..	..	....	..	..	....	..	..	....	61	9	1496
1913	..	..	....	..	..	....	..	..	....	85	11	1548
1914	..	..	....	..	..	....	..	..	....	64	24	1545
1915	..	..	....	..	..	....	..	..	....	33	17	1477
1916	..	..	....	..	..	....	..	..	....	23	5	1425
1917	..	..	....	145	29	2051	..	..	....	22	18	2045
1918	..	..	....	23	26	2127	..	..	....	19	15	2662
1919	..	..	....	88	34	2793	..	..	....	20	20	1989
1920	..	..	....	114	50	3093	..	..	....	39	16	1931
1921	..	..	....	89	51	2102	..	..	....	27	10	1883
1922	38	14	2223	98	56	2367	..	..	....	26	5	2154
1923	27	17	2225	66	20	2098	..	..	....	36	14	2516
1924	28	19	2319	80	38	1940	..	..	....	31	11	2228
1925	44	9	2316	43	..	2203	130	13	2937	44	4	2434
1926	..	14	3182	..	..	....	..	4	2932	..	7	2548
1927	..	11	3446	..	..	....	..	10	3001	..	22	2601
1928	..	9	3650	..	..	....	..	20	3271	..	14	2884
1929	..	8	3545	..	..	....	..	5	3324	..	21	2916
1930	..	8	1956	..	..	....	..	6	3164	..	19	3006
1931	..	7	1647	..	..	....	..	6	3306	..	7	3205
Av. ratio	1:66	1:228		1:27	1:61		1:22	1:342		1:48	1:165	

	Montreal General, Montreal.			City, Cleveland.			Harper, Detroit.			Toronto General, Toronto.		
	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA
1910	..	..	....	..	..	....	..	..	....	..	..	....
1911	..	..	....	..	..	....	..	..	....	..	..	....
1912	..	..	....	..	..	....	..	..	....	..	..	....
1913	..	..	....	..	..	....	..	..	....	..	..	....
1914	..	..	....	..	..	....	..	..	....	..	..	....
1915	..	..	....	..	..	....	..	..	....	..	..	....
1916	..	..	....	..	..	....	..	..	....	..	..	....
1917	..	..	....	..	..	....	..	..	....	..	..	....
1918	..	..	....	..	..	....	..	..	....	..	..	....
1919	..	9	1466	..	..	....	..	..	....	..	..	....
1920	49	15	1647	..	58	1265	..	23	1739	..	..	....
1921	40	14	1477	47	105	1216	..	10	1434	18	..	2333
1922	46	10	1463	26	34	1378	..	30	1561	20	..	2277
1923	24	7	1590	57	37	1315	9	30	1561	40	..	2883
1924	43	9	1325	63	40	1468	16	12	1400	55	..	2612
1925	..	4	1302	78	85	1905	10	5	1549	38	..	2674
1926	..	5	1363	..	41	2354	..	12	1311	..	..	....
1927	..	5	1437	..	29	2339	..	10	1301	..	17	1854
1928	..	5	1577	..	29	2440	..	16	1566	..	18	2047
1929	..	6	1629	..	29	2274	..	10	2089	..	27	2275
1930	..	11	1596	..	38	2192	..	9	1967	..	13	2251
1931	..	8	1930	..	38	2345	..	9	1838	..	11	2249
Av. ratio	1:37	1:181		1:26	1:39		1:129	1:109		1:74	1:124	

	Presbyterian, New York.			Massachusetts General, Boston.			Peter Bent Brigham, Boston.			San Francisco, San Francisco.		
	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.
1910	..	..	....	60	4	2209	..	..	....	..	..	....
1911	..	..	....	51	15	2508	..	..	....	..	..	....
1912	..	..	....	76	14	2654	..	..	....	..	..	....
1913	..	..	....	52	11	2511	..	4	694	..	..	....
1914	..	..	....	27	8	2470	40	1	1744	..	..	....
1915	42	..	1473	24	13	2735	36	10	1754	..	..	....
1916	56	25	1807	31	24	2618	45	24	1952	..	..	....
1917	55	24	1849	32	22	2487	35	20	1898	..	..	....
1918	35	11	1798	37	11	2711	38	31	2369	..	..	....
1919	50	15	2256	24	14	2462	22	15	2476	..	25	1482
1920	55	9	1897	19	15	2443	17	6	2463	29	23	1684
1921	60	12	1832	32	36	2679	20	8	2365	30	15	1657
1922	50	22	1827	40	16	2765	31	7	2668	32	20	1720
1923	67	17	1584	18	15	2570	30	9	2573	36	14	1636
1924	101	33	1704	34	15	2752	39	7	2331	34	33	2020
1925	104	18	1688	32	12	2790	48	6	2026	30	23	2155
1926	..	..	....	..	34	3003	..	6	2167	..	22	2111
1927	..	..	....	..	28	3290	..	13	2421	..	18	2314
1928	..	..	....	..	15	3408	..	11	2264	..	18	2356
1929	..	..	....	..	18	3260	..	2	2274	..	..	....
1930	..	..	....	..	13	3047	..	10	1996	..	..	....
1931	..	..	....	..	15	2980	..	5	1980	..	..	....
Av. ratio	1:29	1:98		1:70	1:164		1:68	1:207		1:36	1:90	

* RF, yearly number of cases of rheumatic fever; AN, of acute glomerulonephritis; MA, of total admissions to the medical wards.

TABLE 1.—RHEUMATIC FEVER, ACUTE NEPHRITIS AND TOTAL ADMISSIONS TO MEDICAL WARDS IN 24 HOSPITALS IN THE UNITED STATES AND CANADA*—*Continued.*

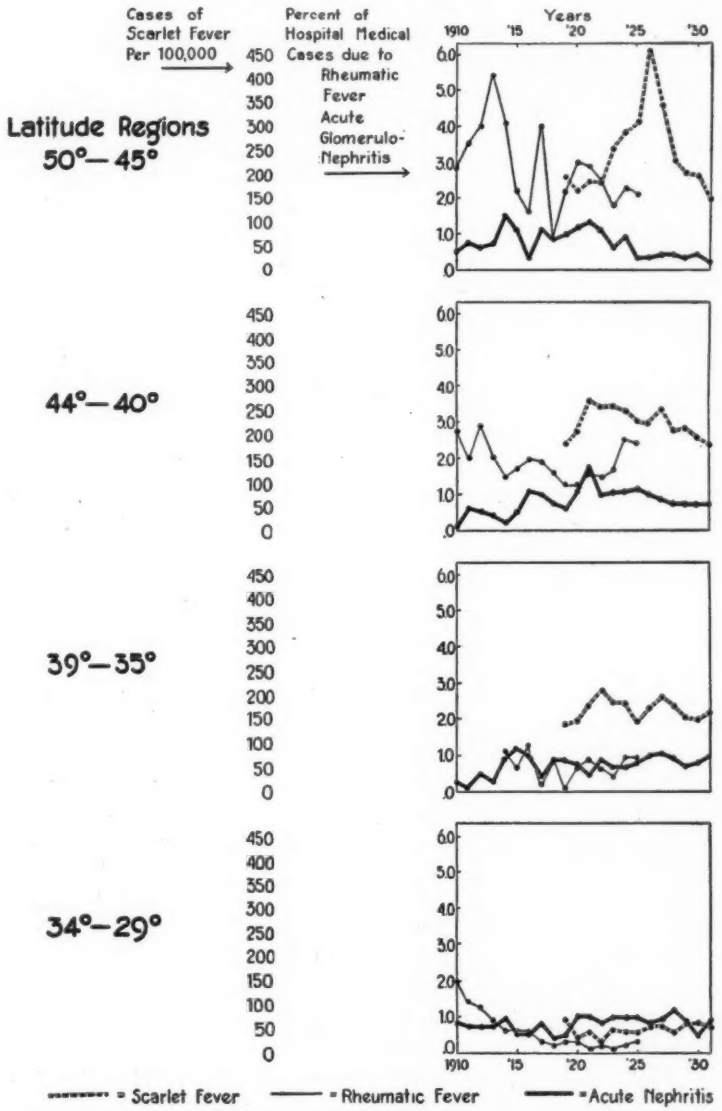
	Denver General, Denver.			State University, Oklahoma City.			Kansas City General, Kansas City, Mo.			City No. 2 (Col.), St. Louis.		
	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.
1910	..	..	....	..	..	....	..	..	....	..	..	....
1911	..	..	....	..	..	....	..	..	....	..	..	....
1912	..	..	....	..	..	....	..	..	....	..	..	....
1913	..	..	....	..	..	....	..	..	....	..	..	....
1914	..	..	....	..	..	....	..	..	....	..	..	....
1915	..	..	....	..	..	....	..	..	....	..	..	....
1916	..	..	....	..	..	....	..	..	....	..	..	....
1917	..	..	....	..	..	....	..	..	....	..	..	....
1918	..	..	....	..	..	....	..	..	....	..	..	....
1919	..	..	....	..	..	....	..	..	....	..	..	....
1920	..	..	....	..	..	....	2	9	1423	6	..	1210
1921	..	..	....	..	..	....	9	6	1546	7	..	1482
1922	..	..	....	1	13	1780	3	15	1788	8	..	1485
1923	..	..	....	2	8	1376	3	11	1849	0	..	2017
1924	19	16	1205	0	2	1463	9	12	1906	20	3	2584
1925	39	11	1181	0	1	1398	3	11	1916	18	2	2439
1926	..	8	569	..	10	1223	..	5	2144	..	36	2439
1927	..	13	714	..	8	1208	..	15	2390	..	42	2393
1928	..	12	940	..	24	1420	..	9	2622	..	..	....
1929	..	8	879	..	5	1456	..	5	2295	..	37	2735
1930	..	16	825	..	11	2076	..	8	2713	..	33	3216
1931	..	13	990	..	2	2130	..	6	2403	..	47	5210
Av. ratio	1:41	1:75		1:2006	1:184		1:359	1:223		1:190	1:105	

	Memphis General, Memphis, Tenn.			Baptist Memorial, Memphis, Tenn.			Louisville City, Louisville, Ky.			Johns Hopkins, Baltimore.		
	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.
1910	..	..	....	..	..	....	..	..	....	..	5	1670
1911	..	..	....	..	..	....	..	..	....	..	2	1650
1912	..	..	....	..	..	....	..	..	....	..	9	1775
1913	..	..	....	..	..	....	..	..	....	..	6	1722
1914	..	..	....	..	..	....	..	..	....	19	14	1723
1915	..	..	....	..	..	....	..	..	....	10	21	1626
1916	..	..	....	..	..	....	..	..	....	22	17	1635
1917	..	..	....	..	..	....	..	..	....	5	8	1811
1918	..	..	....	..	..	....	..	..	....	17	17	1946
1919	..	..	....	..	..	....	..	..	....	2	6	2056
1920	..	..	....	2	..	1264	..	..	....	8	8	1941
1921	..	..	....	2	..	1285	..	..	....	21	9	1844
1922	10	20	1538	4	..	1452	..	..	....	19	9	1948
1923	4	16	2273	3	..	1705	..	..	....	9	12	1887
1924	10	5	1927	5	..	2030	27	..	1352	15	9	1814
1925	9	20	1872	2	..	1760	19	..	1177	34	24	1898
1926	..	13	1381	..	31	2277	..	..	....	..	..	....
1927	..	10	1338	..	34	2398	..	21	1392	..	..	....
1928	..	10	1681	..	37	2934	..	22	1500	..	..	....
1929	..	22	1807	..	16	3728	..	5	1773	..	..	....
1930	..	17	1718	..	19	2103	..	9	2024	..	..	....
1931	..	23	2212	..	36	1873	..	30	1929	..	30	2033
Av. ratio	1:230	1:113		1:527	1:88		1:55	1:99		1:122	1:150	

	Baylor, Dallas, Texas.			John Sealey, Galveston, Texas.			Charity, New Orleans.			Touro Infirmary, New Orleans.		
	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.
1910	..	..	....	..	3	564	91	39	4537	..	..	....
1911	..	..	....	..	3	725	67	38	4600	..	..	....
1912	..	..	....	..	..	806	65	38	5102	..	..	....
1913	..	..	....	..	5	654	49	39	5477	..	..	....
1914	..	..	....	..	3	842	41	68	6368	..	..	....
1915	..	..	....	0	1	1080	54	43	6720	..	..	....
1916	..	..	....	0	3	1061	49	39	6765	..	..	....
1917	..	..	....	0	7	1031	32	63	7637	..	..	....
1918	..	..	....	0	4	1510	24	39	8553	..	..	....
1919	0	8	1691	0	5	875	26	34	6025	..	..	....
1920	2	11	1983	1	6	908	23	76	5181	..	..	....
1921	2	10	1516	0	13	807	7	56	5332	..	..	....
1922	1	6	1645	2	8	892	15	48	5042	..	..	....
1923	1	11	1936	1	27	805	9	49	5842	..	..	....
1924	5	12	2173	1	35	904	21	59	6805	2	16	1334
1925	9	9	2423	4	20	976	32	62	7620	2	36	1598
1926	..	4	1385	..	14	1132	..	..	....	..	19	1670
1927	..	6	1189	..	8	982	..	..	....	..	23	1590
1928	..	8	1044	..	4	977	..	..	....	..	36	1899
1929	..	9	1696	..	9	931	..	..	....	..	20	1826
1930	..	2	1511	..	8	840	..	..	....	..	13	1740
1931	..	7	1878	..	8	938	..	..	....	..	25	1326
Av. ratio	1:668	1:214		1:1205	1:100		1:161	1:122		1:733	1:69	

* RF, yearly number of cases of rheumatic fever; AN, of acute glomerulonephritis; MA, of total admissions to the medical wards.

pitals and consist of the total number of cases reported by the hospitals in each latitude group for each year, and the total number of medical admissions for that same year. The graph shows that the



case frequency of scarlet fever diminishes from latitude region 50–45 degrees to latitude region 34–29 degrees. A similar diminution in frequency exists for the hospital medical admission rate for

rheumatic fever. In contrast to this fact, the hospital medical admission rate for acute nephritis is relatively uniform in the four latitude regions studied.

Comment. The majority opinion at present is that the etiologic agent in scarlet fever is the hemolytic streptococcus. Increasing evidence[3] suggests that the hemolytic streptococcus plays an important rôle in the mechanism of rheumatic fever. The clinical and biologic studies of many workers, notably Longcope[4] and his associates, would ascribe a chief etiologic rôle in acute nephritis to the hemolytic streptococcus. Additional evidence in favor of this concept is found in the observation by Seegal and Lyttle[5] that 20 out of 22 consecutive cases of acute glomerulonephritis studied in New York City showed a significantly high titer of a hemolytic streptococcus antibody termed antistreptolysin by Todd.[6]

It is of interest, therefore, to note the variation in the geographic distribution of these diseases on the basis of the limited statistics available for this study. No explanation is at hand as yet to account for the failure of the hospital incidence of acute glomerulonephritis to follow the type of geographic distribution illustrated by the curves of the two other diseases studied.

Owing to the possibility that agents other than the hemolytic streptococcus may have been responsible for the frequency of cases of acute glomerulonephritis in the southern hospitals, a special study was undertaken to determine this point. The conclusions drawn from the unpublished observations show that much the same type of preceding infection, initiated by the hemolytic streptococcus, occurs in the southern as in the northern patient with acute glomerulonephritis.

Summary. 1. A comparative study has been made of the geographic distribution in North America of acute glomerulonephritis, rheumatic fever and scarlet fever.

2. The case rate for scarlet fever diminishes progressively from latitude region 50–45 degrees to 34–29 degrees.

3. The yearly hospital medical admission rate for rheumatic fever in 24 hospitals shows a similar decrease in the same latitude regions.

4. In contrast to the diminished case frequency of scarlet fever and rheumatic fever in southern latitudes as compared to northern latitudes, the yearly hospital medical admission rate for acute glomerulonephritis does not vary significantly in the four latitude regions studied.

5. The failure of acute glomerulonephritis to diminish in frequency in southern latitudes might be interpreted as supporting the hypothesis that agents other than the hemolytic streptococcus play the chief etiologic rôle in this disease. This does not seem likely, however, since considerable evidence is available incriminating the hemolytic streptococcus as the main incitant of the disease.

6. Since evidence is available ascribing etiologic significance to the hemolytic streptococcus in all three diseases studied here, the variation in the geographic distribution of these diseases based upon the limited data presents a problem in specific host and bacterial interaction.

We wish to express our gratitude to the administrative and medical staffs of the many hospitals that have generously contributed the data upon which much of this study is based.

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ISOLATED TRICUSPID STENOSIS OF PROBABLE RHEUMATIC ORIGIN.

REPORT OF A CASE WITH UNUSUAL CLINICAL AND PATHOLOGICAL FINDINGS.

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STENOSIS of the tricuspid valve is by far the most infrequent of valvular lesions and, according to a very comprehensive review of the literature by Zeisler[1] in June, 1933, there have been only about 250 cases of acquired tricuspid stenosis reported to date. In view of this rarity the following case is presented.

Case Report. H. C., a white female, aged 24, single, was admitted September 1, 1934, to this hospital on the medical service of Dr. Henry Schumer, with the clinical diagnosis of acute cardiac decompensation, mitral stenosis, pulmonary edema and vasomotor collapse.

Family History. Negative for heart disease and tuberculosis.

Past Personal History. Negative for rheumatic fever or any of its manifestations, scarlet fever or other of the acute infections. She had always been pale and sickly as a child, had had a poor appetite, but repeated physical examinations were negative. There was no evidence of cyanosis in childhood and no dyspnea on exertion, but the patient complained of tiring easily.

Present Illness. This dates back to 8 years before admission. While swimming, patient suddenly became weak and cyanotic and had a slight

bloody expectoration. She was confined to bed for several weeks and parents at this time were told that she had a heart murmur. Following this there was noted cyanosis of the lips on exertion. This progressively increased and she also had frequent attacks of hemoptysis, the amount of blood varying from a few drops to a tablespoonful. There was no constant cough. Her general condition was fairly good until about 2 years ago when she developed congestion of the lungs. There was evidence at this time of cardiac decompensation from which she recovered. Since then she had been practically bedridden. One year ago she developed marked edema of the lower extremities with slight swelling of the face and neck. This condition cleared up with rest in bed.

On the day before admission the patient became extremely cyanotic and orthopneic and exhibited signs of peripheral circulatory failure. The pulse was imperceptible and the arterial blood pressure was not obtainable. On admission the heart sounds were distant, irregular and rapid. A soft pre-systolic murmur was heard over the entire precordium, being loudest over the mitral area and a pre-systolic thrill was felt over a corresponding region. Many sibilant and sonorous râles were heard at both bases of the lung. The cervical veins did not pulsate. The abdomen was distended and a fluid wave was obtained. The liver edge was felt two finger breadths below the costal margin, but did not pulsate. The extremities were cold and clammy and there was no edema. The leukocyte count was 20,400, of which 66% were mature granulocytes and 15% young or band forms. In view of her moribund condition, additional laboratory tests were not done, nor was a Roentgen ray taken. The cyanosis and dyspnea increased, the patient became anuric, developed Cheyne-Stokes' respiration with a gallop rhythm and expired the day after admission.

Relevant Postmortem Findings. A somewhat frail figure of fair nourishment, with marked cyanosis. The gross anatomic findings were: 1, Tricuspid stenosis; 2, mitral insufficiency; 3, chronic adhesive pericarditis; 4, hydropericardium; 5, subepicardial hemorrhages; 6, subendocardial degeneration; 7, advanced sclerosis of the lesser circulation; 8, ulcerative plaques in the pulmonary arteries; 9, chronic pulmonary tuberculosis; 10, cirrhosis of the liver; 11, hemangioma of the liver; 12, congested spleen; 13, exaggerated duodenal band; 14, cortical cyst of the right kidney; 15, ascites.

Heart. The pericardial sac was adherent to the dome of the diaphragm posteriorly. There was about 100 cc. of straw-colored fluid in the pericardial cavity. The heart itself was normal in position and measured 11 by 11 cm. in its greatest diameters. There were a few subepicardial hemorrhages noted, these being most prominent in the region of the auriculoventricular sulcus. The musculature was of normal color. There were no gross lesions in the papillary muscles, chordæ tendineæ or columnæ carnæ. The tricuspid valve, when viewed from its auricular aspect, was funnel-shaped. Its walls were smooth and it opened into the ventricle by an elliptical, smooth orifice, which measured 6 mm. in its longest diameter. The walls were somewhat thickened and inelastic, but there was no evidence of scarring or of chronic or recent vegetations (Fig. 1). Because of the non-pliability of the walls of the tricuspid valve, it was believed to be incompetent as well as stenotic. Histologically, there was marked fibrosis with some myxomatous degeneration and areas of vascularization, but no cellular exudate or signs of an active process (Fig. 2). The right auricle showed but a slight degree of hypertrophy and dilatation. The pulmonary valve showed slight atheromatous changes of the valve margins. The mitral valve was dilated and apparently insufficient, admitting 4 fingers, and there was slight sclerosis of the leaflets, especially of the more posterior one, but there was no evidence of stenosis. The aortic valve showed a marked degree of atheromatous change, extending for a few centimeters into the arch with

no evidence of stenosis. The left auricle exhibited marked hypertrophy and dilatation, especially the latter, measuring 9 by 6 cm. when the walls were distended. The auricular musculature was markedly fasciculated.

Serial sections of the myocardium to determine whether Aschoff bodies were present showed them in the wall of the left ventricle (Fig. 3). These consisted of a submiliary accumulation of large mononuclear cells, resembling plasma cells, both morphologically and in their staining qualities, together with some lymphoid cells. These were distributed in a spindle-shaped arrangement usually about the wall of a small radicle of the coronaries, most commonly found in the musculature of the left auricle and about the coronary vessels in the auriculoventricular sinus. Similar lesions were also found in other organs of the body.

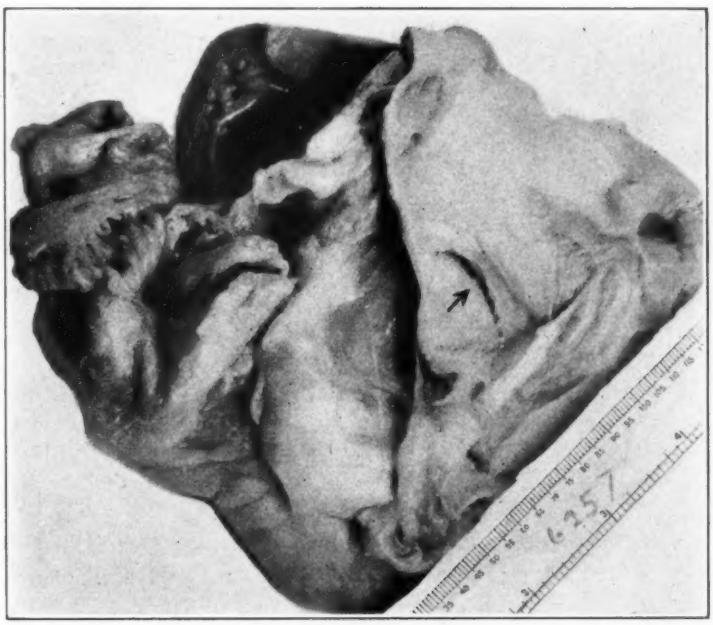

FIG. 1.—Arrow points to the auricular aspect of the stenotic lesion present at the tricuspid orifice.

Lungs. There were several submiliary calcified areas in the region of the right apex which on section showed healed peribronchial tuberculosis. There was bronchopneumonia at both bases.

The pulmonary artery showed marked sclerosis in all of its radicles with advanced atheromatous changes in the larger vessels (Fig. 4). There was an area of beginning necrosis near the division of the main artery on the right side upon which was superimposed a recent adherent 2 cm. thrombus. There was an ulcerated ovoid area, 3 by 2 cm., at the point of division of of the left main artery (Fig. 5). There was no discernible sclerosis in the greater circulation.

Liver. In spite of its apparent enlargement clinically, the liver was definitely smaller than normal, being contracted, firm and nodular and measured 20 by 14 cm. in its largest diameters. There was a small dark bluish circumscribed hemangioma on the anterior surface, near the inferior

FIG. 4.—Cut surface of pulmonary tissue showing extreme vascular sclerosis, the mouths of the vessels projecting prominently.

FIG. 5.—Ulcerated plaque in the left main pulmonary artery near its bifurcation.

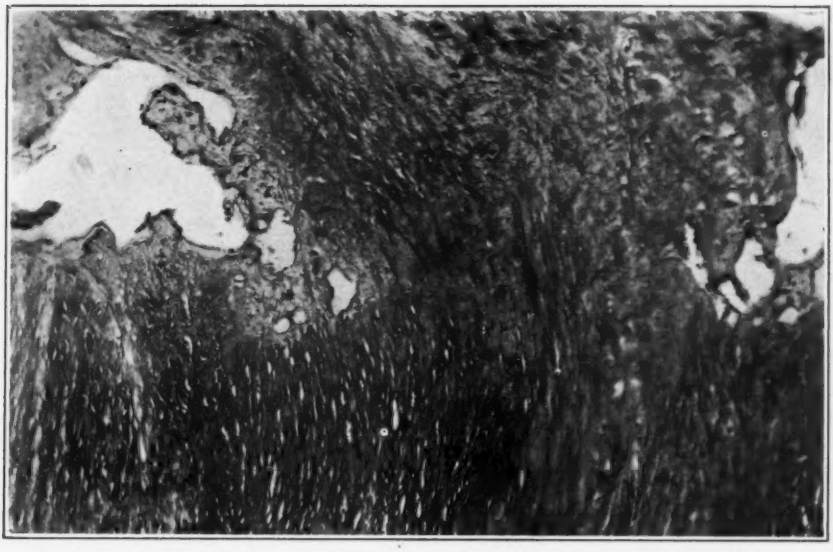

FIG. 2.—Section through the tricuspid valve showing marked fibrosis with some myxomatous degeneration and areas of vasularization.

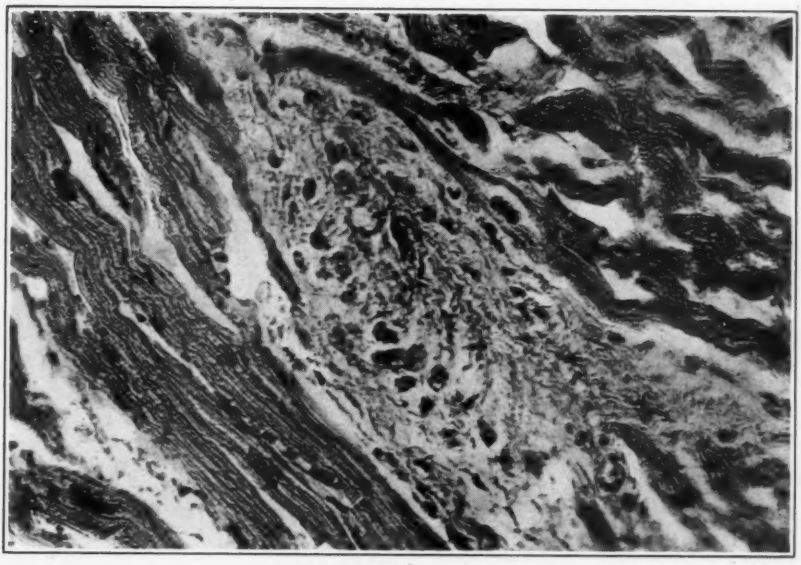

FIG. 3.—Aschoff lesion in the wall of the left ventricle.

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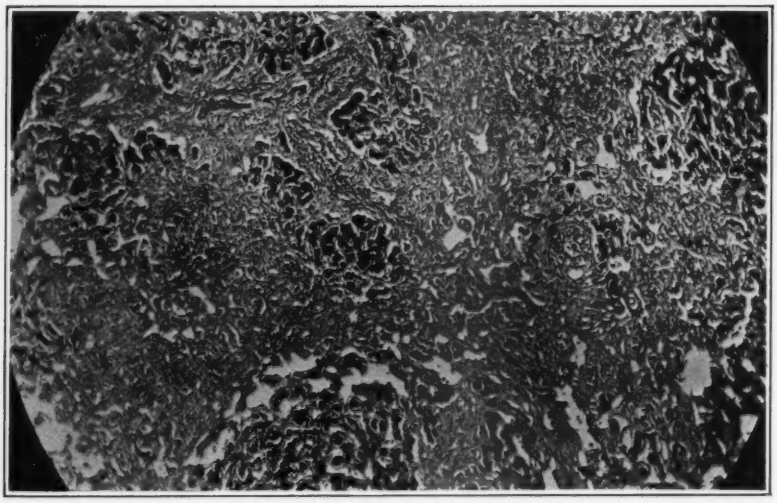

FIG. 6.—Section of liver showing extensive cirrhosis. Only scattered islands of atrophic liver parenchyma remain intact.

border of the right lobe, measuring 8 mm. in diameter and extending for about 3 mm. into its substance. On section, the liver showed an extreme degree of cirrhosis, spreading diffusely throughout the lobules. Microscopically, there was marked periportal cirrhosis with congestion about the central veins (Fig. 6). The hepatic veins were dilated. There were about 2000 cc. of thin serosanguinous fluid free in the peritoneal cavity.

Discussion of Tricuspid Stenosis. *Degree of Stenosis.* The circumference of the adult tricuspid ostium varies normally between 10 and 12 cm. according to White,[2] and this valve is regarded as stenotic if its orifice measures 8 cm. or less. Usually, the stenosis is not present to a marked degree. Functionally, the right heart, including its auriculoventricular valve, is relatively passive and may be considered as an adjuvant of the venous system. The pressure normally exerted on the tricuspid valve is low as compared to that on the mitral valve which is subjected to the stress and strain of the much more active left heart. Kerr and Morrison[3] offer as an additional explanation for the relatively slight degree of stenosis seen in the tricuspid valve, the triangular shape which prevents its narrowing to the degree seen in mitral stenosis.

Of 30 cases reported by Dressler and Fischer,[4] only 5 showed marked stenosis while their most advanced case barely admitted the passage of the small finger (approximately 1 cm. in diameter). Cottin and Saloz[5] reported a case closely resembling ours anatomically in which a similar degree of stenosis was present. Oigaard[6] described his case as admitting the passage of a pencil (approximately 7 to 8 mm.). The majority of reported cases had a much lesser degree of stenosis; thus Zeisler[1] gives 7.1 cm. as the circumference of the ostium in his case.

Association with Other Valvular Defects. Tricuspid stenosis is rarely a solitary lesion. Of 195 cases compiled by Futcher,[7] in only 14 cases was the tricuspid valve the only one involved while in 104 cases both the tricuspid and mitral were affected. In such instances, the narrowing of the mitral is usually the much more pronounced of the two. This has been the usual finding in other reported series. There may be associated lesions in the other two valves, the common picture being termed "Dreiostienstenose," indicating a combined stenosis of the tricuspid, mitral and aortic valves. In a large percentage of cases, there is a relative, if not actual, tricuspid insufficiency associated with the stenosis as a result of the inability of the stenotic leaflets to approximate each other.

Etiology. The etiology of this condition has been the subject of a great deal of study and investigation. The belief was held formerly that most cases, if not all, were congenital in origin. Careful anamneses have revealed the incorrectness of this belief and now the consensus of opinion is that the great majority are acquired in postnatal life. In many instances no definite etiologic factor can be traced in the history and the appearance of cardiac

symptoms may be the first indication of the presence of a valvular lesion, but this does not imply that the patient was born with a damaged valve. This is emphasized very definitely in our case. Oigaard[6] states that in more than one-half of the cases no etiologic factor is determinable. A congenital lesion usually manifests itself in infancy or early childhood. There is obtainable in such instances a history of cyanosis very early in life and postmortem examination of the heart will often disclose other congenital lesions such as pulmonary stenosis, narrowing of the aorta or defect of the interventricular septum.

In many cases there is present a history of acute articular rheumatism, repeated sore throat, chorea, muscular rheumatism ("growing pains") or other manifestations of a rheumatic affection. Cabot[8] has stressed rheumatic heart disease without a history of so-called rheumatism. Aschoff bodies have been found in the hearts of patients in whom a history of attacks of articular rheumatism was not obtained. Other acute infections such as scarlet fever, typhoid fever and puerperal sepsis may be the inciting causes. An apparently truly congenital case has been reported by Cottin and Saloz[5] where cyanosis appeared very early in infancy, became more pronounced as the child grew older with development of clubbing of the fingers. An antemortem diagnosis of tricuspid stenosis was made, based on classical physical findings and this was substantiated at necropsy. In their discussion, these authors differentiate between a congenital malformation of the valve and fetal endocarditis and conclude that the latter is the more plausible explanation in their case.

Often the macroscopic appearance of the valve makes one suspect a congenital origin when the valve edges are smooth and grossly resemble a malformation without the irregular appearance of cicatrization that we usually see following endocarditis. However, it is only when there is no history of predisposing infection, when cyanosis appears early in life, when serial sections of the myocardium fail to show the presence of Aschoff bodies, and especially if there are present other lesions that are usually considered congenital that the diagnosis of a congenital lesion can be made.

Our first impression on examining the tricuspid valve was that we were dealing with a congenital lesion that had gone unrecognized for a long time and had only become clinically evident after an acute illness. The complete absence of a history of rheumatic infection or other possible etiologic factors, together with the smooth appearance of the valve walls that showed no evidence of leaflets, nor of inflammatory reaction and resembled grossly a malformation, strongly suggested a prenatal affection. On the other hand, there were no other congenital deformities, nor was there present a history of cyanosis during infancy. The finding of Aschoff bodies

made a rheumatic cause for the valve lesion the most likely, even though it showed no active signs postmortem.

Other unusual features of this case were the absence of pulsation of the cervical veins, the relatively normal size of the right auricle and the sclerosis of the lesser circulation. We shall not enter into a discussion in this presentation of sclerosis of the lesser circulation of which we have apparently an example, but we believe that the two conditions are independent and cannot be explained on a single clinicopathologic basis. There was no evidence, microscopically, that the sclerosis was rheumatic in origin. The clinical picture was at no time characteristic and in this particular case, it seems impossible to have made a diagnosis of tricuspid stenosis before death. However, this condition should be borne in mind and suspected, especially in cases of rheumatic heart disease where the physical signs are localized to the region of the xiphoid process of the sternum.

Thus we have here an example of a rheumatic lesion involving principally one valve and not preceded by the usual symptoms which we have been accustomed to call rheumatism. The pallor, fatigability, anorexia and weakness of the patient as a child were probably rheumatic manifestations, as brought out recently by Kaiser[9] and termed by him "minor rheumatic manifestations." The disease left its imprint on the heart musculature in the form of rheumatic nodules or Aschoff bodies, and on the tricuspid valve, causing extreme stenosis.

The small, nonpulsating liver was another surprising and unusual feature of this case, but some light was thrown on this by the gross and microscopic appearance of this organ, the cirrhosis being so marked in degree that it caused a contracture of the liver parenchyma, especially in region of the portal spaces and prevented stasis of blood in the radicles of the portal vein.

Summary. The case of tricuspid stenosis reported presents the following noteworthy features:

1. The extreme degree of narrowing of the tricuspid ostium, resulting in a valve grossly resembling a malformation rather than the end result of an inflammatory process.
2. The absence of involvement of the other valves, except for a mitral insufficiency and slight sclerosis.
3. The absence of an etiologic factor in the history, except for so-called minor rheumatic manifestations.
4. The finding of Aschoff bodies in the myocardium indicating the presence of rheumatic heart disease.
5. The indistinguishability clinically from mitral stenosis.
6. The absence of a pulsating liver and distention of the cervical veins.
7. The slight enlargement of the right auricle in face of the extreme stenosis.

8. The finding of advanced lesser circulation sclerosis, apparently an independent lesion.

The author is indebted to Dr. Joseph Felsen, Director of Laboratories, Bronx Hospital, for his kind assistance in the preparation of this paper, and to Dr. Henry Schumer for permission to include the clinical findings of this case.

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VARIABILITY OF MURMURS IN MITRAL STENOSIS.

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Mitral stenosis was first mentioned in the literature by Mayow[8] in 1669. The first definite knowledge concerning it appeared in 1715 in Vieussens'[14] treatise on the heart. No mention of cardiac murmurs is found in the first comprehensive textbook on heart disease written by De Senac.[5] Corvisart[3] described the palpable thrill of mitral stenosis in 1806. In 1826 Laennec[10] first described the murmurs of mitral stenosis, one as a dull bruit quite like the sound produced by a file rubbing on wood, and followed by a loud bruit somewhat rough and harsh. Hope[9] first noted the variability of the murmurs when he described bruits audible in slow and rapid hearts with mild to severely stenosed mitral valves. He designated this rasping bruit as a diastolic murmur. Bertin[1] confirmed Laennec's descriptions of the murmurs, and further suggested that two distinct bruits were audible. Williams[16] modified Hope's description of the murmurs, but also classified it as being diastolic in the cardiac cycle. Bouillaud[2] established the relationship of rheumatic fever to mitral stenosis; this had been mentioned by Pitcairn in 1788 and by Corvisart in 1806. Fauvel[6] called the murmur presystolic, but added that this was not a positive sign of mitral stenosis. The tradition of a presystolic murmur essential

to the diagnosis of mitral stenosis persisted for many decades. In the second Herter Lecture in 1914, Lewis[12] stated that the murmurs which accompany mitral stenosis in different patients are very variable in their time relations and that they not only vary also greatly from cycle to cycle in the same patient but even vary both in time and quality. Crummer[4] simply stated that no single murmur is constant or characteristic of mitral stenosis. White[15] indicated that if we should rely on the presence of a presystolic murmur for a diagnosis of mitral stenosis we should miss at least half the cases of this valvular lesion.

This study indicates the importance of the variability of the murmurs in 237 cases of mitral stenosis. These 237 patients constituted 14.4% of a larger group of 1646 adults with organic heart disease seen in the Cook County Hospital.[7] None of the patients in this report had any evidence of aortic insufficiency, hypertension, or thyrotoxicosis. Their ages varied from 15 to 68 years; 80% were 20 to 50 years old; the largest group (35.4%) was 31 to 40 years old. Auricular fibrillation was present in 110 patients (46.6%).

The murmurs were recorded to indicate the time in the cardiac cycle where each appeared best sustained. Six different groups were noted, which included, according to their frequency, the following: systolic-diastolic, systolic, presystolic-systolic, no murmurs audible, diastolic, and presystolic murmurs.

Systolic-diastolic Murmurs. These were audible in 159 (67.08%) of the 237 cases. The loud, rasping to-and-fro murmurs occupied the entire cardiac cycle. The bruits were most often localized to a small area surrounding the apex of the heart, but occasionally were audible over the whole precordium. Seventy-three (46%) of the 159 patients had auricular fibrillation and the characteristic rasping sound of the murmurs was unchanged. The exact timing of the murmurs was difficult, due to the rapid cardiac rate and the frequent changes in the irregularity. These were designated systolic-diastolic murmurs because the bruits were the longest, loudest and harshest of all the murmurs noted.

Systolic Murmur. The systolic murmur was present alone in 36 cases (15.2%), of which 23 (64%) had auricular fibrillation. This murmur was audible over the entire precordium in all 36 patients. The bruit was loud and intense in each instance.

Presystolic-systolic Murmurs. Twenty-eight patients (11.8%) presented a short, loud, rasping, crescendo murmur followed by a long, loud, clear bruit. The rhythm was regular in 24 and auricular fibrillation was present in the other 4 patients.

No Murmurs Audible. Eight patients (3.37%) with auricular fibrillation were in this group. The heart was auscultated frequently, but in each case no murmur was discernible. Lewis[13] emphasized this when he stated that in auricular fibrillation, mitral stenosis may be concealed, the heart at times presenting no murmurs.

TABLE 1.—MURMURS IN THE 237 CASES OF MITRAL STENOSIS.

	Cases.	White male.		White female.		Colored male.		Colored female.		Totals.	
		R.*	AF.†	R.	AF.	R.	AF.	R.	AF.	R.	AF.
1. Systolic-diastolic	159 (67.08%)	43	39	22	33	10	0	11	1	86	73
2. Systolic	36 (15.3%)	6	13	4	9	1	0	2	1	13	23
3. Presystolic-systolic	28 (11.8%)	11	3	4	1	6	0	3	0	24	4
4. No murmurs	8 (3.3%)	0	5	0	2	0	0	0	1	0	8
5. Diastolic	3 (1.26%)	1	1	0	1	0	0	0	0	1	2
6. Presystolic	3 (1.26%)	1	0	2	0	0	0	0	0	3	0
Totals	237 (100%)	62	61	32	46	17	0	16	3	127	110
		123		78		17		19		237	
		84.8%				15.2%				100%	

* Regular rhythm.
† Auricular fibrillation.

Diastolic Murmur. This short rasping murmur was audible in 3 cases (1.26%); 2 had auricular fibrillation.

Presystolic Murmur. This bruit occurred with the same frequency as the diastolic murmur. The cardiac rate and rhythm were regular in each case. The diastolic and presystolic murmurs of mitral stenosis occurred alone only 6 times (2.52%) in this group of 237 patients. The rarity was surprising as compared with the teachings prevalent concerning the characteristic murmurs of mitral stenosis.

Comment. There were 76 deaths (32%) during the period of this study. The murmurs audible had no apparent relation to the mortality. Auricular fibrillation also seemed to have little influence on the outcome. Of the 110 patients with auricular fibrillation, the frequency with which the murmurs occurred was approximately the same as in those with regular sinus rhythm. In these cases the murmurs and the frequency of their occurrence was as follows: Systolic-diastolic, 66.3%; systolic, 20.9%; presystolic-systolic, 3%, and diastolic, 1.8%. The other 8 (7.2%) were the patients with no murmurs audible. Auricular fibrillation was infrequent in the colored patients with mitral stenosis. Of the 36 colored patients, 17 males and 19 females, auricular fibrillation occurred in 3 of the females and not at all in the males.

The incidence of double murmurs, systolic-diastolic and presys-

tolic-systolic, was 79%. All of the murmurs mentioned, whether single or double, were immediately recognized by the characteristic rasping sound, audible even to the untrained ear. The loud systolic murmur was present alone in 15.2%. The combination of auricular fibrillation and a loud systolic murmur audible over the entire precordium, in the absence of thyrotoxicosis or hypertension, was evidence of mitral stenosis. Levine[11] stated that loud systolic murmurs are always associated with cardiovascular disease. Lewis[13] advised that less effort be expended on learning to time the murmurs of mitral stenosis and more energy be applied to recognizing the characteristic sound, like knowing the bark of a dog. The marked variability of the murmurs of mitral stenosis, as noted in the literature and as indicated in this study, suggest the general acceptance of this advice.

Summary. 1. The variability of the murmurs in 237 cases of mitral stenosis is reported.

2. Auricular fibrillation was present in 46.6%; it had no effect on the character or type of murmurs audible.

3. Double murmurs were found in 79%.

4. Systolic murmurs alone were present in 15.2%.

5. The murmurs of mitral stenosis were readily recognized by the characteristic rasping sound without resorting to definitely isolating the murmurs in the cardiac cycle by timing.

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THE VALUE OF COLLOIDAL SULPHUR IN THE TREATMENT OF CHRONIC ARTHRITIS.

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Sulphur in one form or another has been used as a therapeutic agent since ancient times. Only recently, however, has its value in the treatment of chronic arthritis been stressed. Among the earliest papers on the use of colloidal sulphur in the treatment of chronic arthritis are those of Comrie[1] and Cawadias,[2] both of whom report favorable results. In 1927, Race[3] reported favorably on its use in 42 cases treated in the Devonshire Hospital. More recently, the study of the effect of sulphur has been given further impetus. Wheeldon and Main[4] report that, on the basis of 250 cases studied for 2 years, they were convinced that colloidal sulphur had a definite place in the therapeutics of arthritis. Woldenberg,[5] employing colloidal sulphur in the treatment of 100 cases of atrophic arthritis, believed that it had a definite therapeutic value. Senturia[6] reported improvement in 75% of 60 cases, 43 of which were hypertrophic, the rest being either atrophic or mixed types or fibrositis. Sullivan and Hess[7] and Loeper and his associates[8] report good results in a smaller series of cases.

Sulphur metabolism does not come within the scope of this paper, but it should be pointed out that the cystin content of certain structures is considered a reliable guide to the sulphur metabolism of the body. Sullivan[9] recently described a method for estimating the cystin content of the finger nails. Sullivan and Hess,[7] in a study of the finger nails of 105 patients with arthritis, found the cystin content below normal in 65% of the cases. An editorial in the Lancet[10] recently mentioned that Neligan reported he found a low cystin content of the finger nails in 75% of his cases.

Sullivan and Hess[7] applied sulphur therapy to 6 patients with a subnormal cystin content of the finger nails and found that improvement was accompanied by a rise in the cystin content of the finger nails. Woldenberg[5] also reported an increase in the cystin content of the finger nails after colloidal sulphur therapy.

The present study was undertaken not only to evaluate the clinical results of colloidal sulphur therapy in chronic arthritis and its effect

upon certain cellular and immune reactions of the blood, but to ascertain the effect of this form of therapy upon the cystin content of the finger nails and to determine whether the cystin determination is of value in selecting cases for sulphur therapy.

The patients were selected on admission to the clinic without regard to type, severity, age, or duration of symptoms. The usual routine physical and laboratory examinations were made on all patients and the cystin content of the finger nails was estimated according to the method of Sullivan[9] before treatment was instituted. The blood studies included non-filament cell counts, sedimentation rates using Westergren's technique, and red and white blood cell counts. They were also made at varying intervals after treatment. The clinical symptoms were recorded on special charts.[11]

An aqueous solution of colloidal sulphur (Sulisocol) containing 10 mg. per cc. was administered intravenously or intramuscularly twice weekly. No other treatment was given. Since the usual dosage (10 mg. twice weekly) did not produce definite effects, it was increased to 20 mg. twice weekly. In those cases where no improvement was obtained with 20 mg. doses, it was further increased to a maximum of 30 mg. twice weekly. Certain patients who received 10 mg. twice weekly for several weeks and who were not improved were definitely improved when the dose was increased to 20 or 30 mg. A few patients could not tolerate the larger doses.

Symptoms of fatigue, drowsiness, loss of appetite, headaches and increased pain, stiffness or swelling of the joints after the intravenous injection of colloidal sulphur indicate overdosage. In such instances the dose should be reduced but, if the symptoms still persist with the smaller dosage, the intramuscular method should be used instead. If this does not relieve the symptoms, the use of colloidal sulphur should be discontinued. As with vaccine therapy, the optimum dose is characteristic for each individual.

Toxicity. Of 200 patients with arthritis of different types treated with colloidal sulphur during the past 18 months, only a few had severe symptoms of toxicity and they were temporary. A few developed urticaria and scarlatiniform eruptions but these quickly subsided when the medication was discontinued. Some complained of nausea and an occasional patient complained of vomiting, abdominal cramps and diarrhea. Others complained of severe fatigue, headache, drowsiness, heaviness of the eyes, extreme nervousness, generalized muscle soreness and occasionally of insomnia and loss of appetite. A few patients receiving 30 mg. doses had chills and fever which appeared 2 to 4 hours after the injection and they were confined to bed for 24 hours. These reactions did not occur during the first 3 or 4 weeks of treatment. It was concluded, therefore, that these patients had been given an excess of sulphur and that this had caused the reaction. Patients receiving 10 or 20 mg. did not experience reactions of this type. Untoward reactions following

the intravenous administration of sulphur were reduced or were entirely eliminated when it was given intramuscularly. Intramuscular injections did not produce pain, soreness or local reactions. Any symptoms of toxicity quickly disappeared when the medication was terminated.

Controls. Twenty-five patients, consisting of 10 with mixed arthritis, 8 with rheumatoid arthritis and 7 with osteoarthritis, were used for control purposes. Ringer's solution was administered intravenously as placebo medication for from 6 to 8 weeks. This was followed by the intravenous injection of sulphur for the same length of time. Sedimentation rates, non-filament cell counts and red and white blood cell counts were made before, during and at the end of both the control and the test periods.

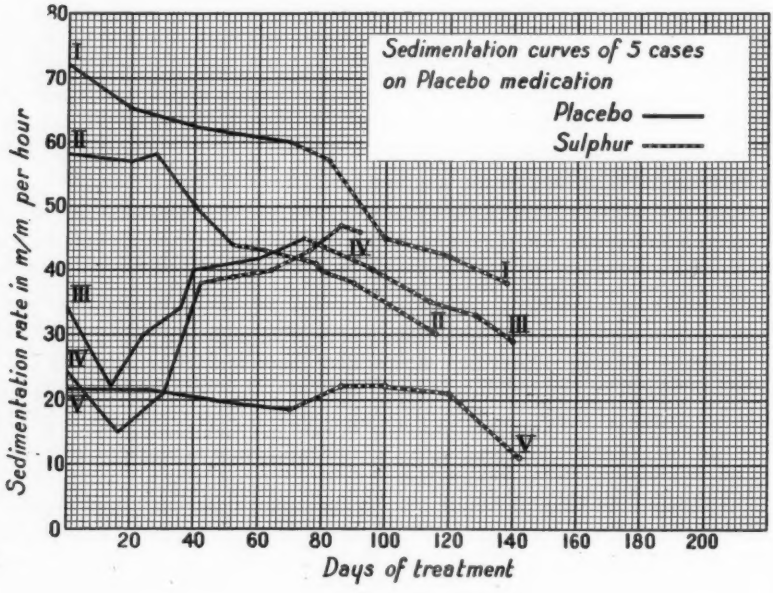

FIG. 1.

With patients receiving placebo medication the mean sedimentation rate was 22.22 mm. before and 21.21 mm. after treatment and the mean non-filament cell count was 15.35% before and 15.12% after treatment. With those patients given colloidal sulphur therapy, the mean sedimentation rate was 23.5 mm. before and 16.9 mm. after treatment and the mean non-filament cell count was 16.12% before and 13.9% after treatment. Although there was only a slight difference between the mean initial and final sedimentation rates and non-filament cell counts following placebo medication, the individual differences were marked. The mean trends were

practically unchanged with placebo medication. Figure 1 illustrates graphically the sedimentation rates of 5 typical cases.

With sulphur therapy the reduction in the sedimentation rate and non-filament cell count was comparatively slight but this was regarded as significant because the initial readings were low.

The Effect of Sulphur Medication Upon the Cystin Content of the Finger Nails. The normal cystin content of the finger nails was considered to be 12 mg. or above per 100 mg. of nails. Twenty-five patients with a subnormal cystin content were studied to determine the quantitative effect of intravenous colloidal sulphur. These

TABLE 1.—THE EFFECT OF INTRAVENOUS SULPHUR THERAPY UPON THE CYSTIN CONTENT OF THE FINGER NAILS.

Case No.	No. of injections	Total mg. of sulphur injected.	Period of treatment (days).	Cystin content in mg. per 100 mg. of nails.		Clinical results.
				Initial.	Final.	
6226–33	27	540	171	7.27	14.28	Improved.
1177–34	10	200	112	7.37	9.73	Improved.
21642	9	110	131	7.88	12.82	Improved.
147–34	15	300	78	8.07	12.18	Unimproved.
14044–33	13	250	151	8.60	12.95	Unimproved.
22674–33	13	250	73	8.96	15.61	Improved.
5380–34	10	200	78	8.98	11.36	Improved.
1816–33	10	200	116	9.74	13.51	Unimproved.
2172	21	310	97	9.82	11.02	Improved.
28465–33	13	260	140	9.88	12.38	Improved.
15645–33	9	90	47	10.33	13.88	Improved.
13356–34	12	240	206	10.37	11.59	Unimproved.
199–34	9	180	78	10.41	12.50	Improved.
2027–34	16	320	72	10.41	11.31	Improved.
19464–33	30	450	170	10.68	13.44	Improved.
11921–34	12	270	117	10.68	12.13	Improved.
1338–34	45	900	193	10.73	14.00	Improved.
12695	18	180	152	10.84	10.87	Unimproved.
13323–34	10	200	81	11.09	12.64	Unimproved.
18097–34	12	220	77	11.11	14.34	Improved.
23918–33	22	300	103	11.30	12.44	Unimproved.
10256–34	17	320	141	11.62	13.00	Improved.
7829	16	340	113	11.80	12.37	Unimproved.
11917–34	22	530	126	11.84	12.50	Unimproved.
17362–34	35	620	144	11.90	12.50	Improved.

patients received a mean of 310.2 mg. of colloidal sulphur over a mean period of 119.56 days. The mean cystin content was 10.07 mg. before and 12.65 mg. per 100 mg. of finger nails after sulphur medication, a mean increase of 2.58 mg. per patient (Table 1). In 21 cases there was a definite increase in the cystin content but in the other 4, it was less than 1 mg. A difference of 1 mg. was not considered an increase because of the possibility that it might be due to experimental error, etc.

An Analysis of the Effects of the Intravenous Administration of Sulphur in 100 Cases. The classification of arthritis described in a previous paper[11] was used in the present study. The 100 cases studied are grouped according to the cystin content of the finger nails and the percentage of improvement in each group considered

separately (Table 2). The criteria of improvement were: 1, improvement in focal symptoms, *e. g.*, reduction of pain, swelling, stiffness, etc.; 2, improvement in constitutional symptoms, *e. g.*, gain in weight, lessening of fatigue, increase in appetite, etc.; 3, reduction in the sedimentation rate and non-filament cell count.

TABLE 2.—RESULTS FOLLOWING INTRAVENOUS SULPHUR THERAPY ARRANGED ACCORDING TO CYSTIN CONTENT OF THE FINGER NAILS.

Cystin content in mg. per 100 mg. of nails.	Types.	No. of cases studied.	Improved.	
			Number.	Per cent.
6 to 7.9	Rheum.	0	0	
	Mixed	2	1	50
	Osteo	2	2	100
	Total	4	3	75
8 to 8.9	Rheum.	3	2	66.6
	Mixed	2	2	100
	Osteo	2	1	50
	Total	7	5	71.4
9 to 9.9	Rheum.	4	3	75
	Mixed	4	2	50
	Osteo	3	3	100
	Total	11	8	72.7
10 to 10.9	Rheum.	8	5	62.5
	Mixed	11	6	55.5
	Osteo	7	5	71.4
	Total	26	16	61.5
11 to 11.9	Rheum.	5	2	40
	Mixed	9	5	55.5
	Osteo	5	1	20
	Total	19	8	42.1
11.9 and above	Rheum.	13	3	23.1
	Mixed	13	4	30.7
	Osteo	7	1	14.3
	Total	33	8	24.2
Grand total		100	48	48

Sixty-seven patients had a cystin content below 12% (Table 2) and 40, (59.7%) were improved; 20 of these had rheumatoid arthritis of which 12 (60%) were improved; 28 patients had mixed arthritis and 16 (57.1%) were improved; while 19 patients had osteoarthritis and 12 (63.2%) were improved. When the cystin content was below normal, the percentage of improvement was essentially similar in all groups.

Of 33 patients with a normal cystin content 8 (24.2%) were improved compared with 40 (59.7%) of the cases with a cystin content below normal.

The Effect of Sulphur Therapy Upon the Sedimentation Rate and Non-filament Cell Count. It was previously shown[12] that the sedimentation rate and non-filament cell count usually are reduced only when there is clinical improvement. The mean sedimentation rate and the mean non-filament cell count were low in this series of patients because most of them had mixed arthritis or osteoarthritis. When the 100 cases are taken as a whole, there is very little change and the mean trend is only slightly affected. In the 48 cases showing improvement, however, there was a reduction of sedimentation rate and non-filament cell count. The mean sedimentation rate was 20.28 mm. before and 14.25 mm. after sulphur medication, a mean reduction of 6.03 mm. The mean non-filament cell count was 15% before and 11.9% after sulphur medication, a mean reduction of 3.1%.

Thus we have a difference of 3.1% between the initial and final mean nuclear counts and a difference of 6.03 mm. between the initial and final mean sedimentation rates. In order to determine that this difference is significant and not due to chance, it is necessary to calculate: 1, the mean; 2, the mean deviation; 3, the standard deviation; 4, the probable error of the mean; and 5, the probable error of the difference.

For these calculations, we have used the standard formulæ as published by Kent.[13]

Standard Deviations: x = initial determinations; y = final determinations. Standard deviation is the constant which has been adopted by biometricians to measure in absolute terms the degree of scatter or dispersion of the variates, or: $s = \sqrt{\frac{S(X)^2}{N}}$ where s = standard deviation, S = sum and X^2 = the squares of the individual deviations from the mean, and N = the number of values in the series, or: $s = \sqrt{\frac{\text{sum of the squares of the individual deviations from the mean}}{\text{number of cases}}}$

Substituting the value of the nuclear count, $s_x = \sqrt{\frac{1204.96}{48}} = \sqrt{25.10} = \pm 5.01$, or the standard deviation of the initial count. $s_y = \sqrt{\frac{594.06}{48}} = \sqrt{12.38} = \pm 3.52$, or the standard deviation of the final count.

Probable Error of the Mean. $PE_m = 0.6745 \times \frac{s}{\sqrt{N}}$, where PE_m = probable error of the mean, s = standard deviation and N = number of values or cases in the series. Substituting the value of the nuclear count, $PE_{mx} = 0.6745 \times \frac{5.01}{\sqrt{48}} = \pm 0.4876$ or the probable error of the mean of the initial nuclear count. $PE_{my} = 0.67449 \times \frac{3.52}{\sqrt{48}} = \pm 0.432$ or the probable error of the mean of the final nuclear count.

Probable Error of the Difference. Pearl[14] states that "the probable error of the difference between any two independent quantities (*i. e.*, quantities such that there is no correlation between their errors) is equal to the square root of the sum of the squares of the probable errors of the quantities entering into the difference," or, *i. e.*, $\sqrt{(PE_mX)^2 + (PE_mY)^2}$ = the probable error of the difference, where PE_m equals the probable error of the mean and X and Y the

independent quantities entering into the difference. In this instance, X equals the initial and Y the final nuclear counts.

Substituting the values of the nuclear count, $\sqrt{(0.4876)^2 + (0.3422)^2} = \pm 0.595$, or the probable error of the difference. According to Pearl[14], "It has been practically a universal custom among biometric workers to say that a difference (or a constant) which is smaller than twice its probable error is probably not significant, whereas a difference (or a constant) which is three or more times its probable error is either 'certainly,' or at least 'almost certainly,' significant." The difference equals the initial mean nuclear count minus the final mean nuclear count, or $15.02 - 11.91 = 3.11$. Therefore, $\frac{3.11}{0.595} = 5.226$, or the difference is over 5 times the probable error of the difference.

Using the same formulæ, the difference between the initial and final mean sedimentation rates is 3.345 times the probable error of the difference.

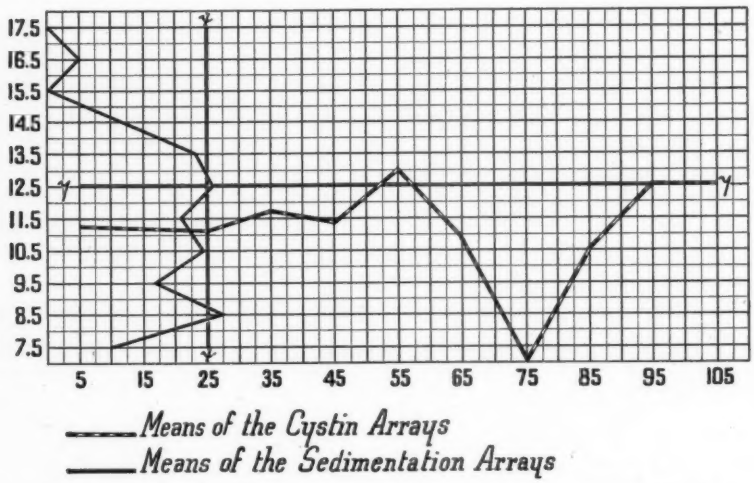

CHART 1.—Observed regression lines showing conclusively the lack of correlation between the cystin content and the sedimentation rate.

We may, therefore, draw the conclusion that the reduction of the sedimentation rate and nuclear count was most certainly significant and not due to chance.

The Correlation Between the Sedimentation Rate and the Cystin Content of the Finger Nails. In a recent article, Argy[15] states that "at least on an average, an inverse ratio between cystin content of the finger nails and sedimentation reaction of the blood does exist in arthritis. This is not true, however, in every instance when individual cases are considered." Only 23 cases were reported, a series too small to be conclusive. We have compared the sedimentation rate and cystin content in 200 cases and have estimated the coefficient of correlation, according to the formulæ of Pearl,[14] in 142 cases. In perfect correlation the coefficient is 1 and the nearer the coefficient approaches 1, the better the correlation.

The coefficient of correlation of our series is 0.0196 which is very poor or almost no correlation. It may be concluded, therefore, that

the sedimentation rate and cystin content are in independent series and are not correlated. Their observed regression lines (Chart I) are practically perpendicular, whereas in correlation they are more or less parallel. This further proves that there is no correlation and that their movements are entirely independent; that is, any movement in the sedimentation rate does not affect the cystin content, and *vice versa*.

When an increase in one series occurs in conjunction with an increase in another series, the correlation is said to be positive and the coefficient of correlation is positive. When an increase in one series occurs in conjunction with a decrease in another series, that is, an inverse ratio, the correlation is said to be negative and the coefficient of correlation is negative. In our series, the coefficient of correlation was: (1) small, indicating that there was no correlation; and (2) positive, indicating that no inverse ratio existed.

The Effect of Sulphur Therapy Upon the White and Red Blood Cell Count. There was only a slight variation in the white blood cell counts in this series. The initial mean count was 7450 and the final mean count was 8180. This variation was not considered significant. The red blood cell counts also showed only minor variations. The initial mean count was 4,370,000 and the final mean count was 4,450,000.

Discussion. The results of the present study, as well as the work of others, indicate that colloidal sulphur produces favorable clinical results in a significant percentage of patients with chronic arthritis. The exact mechanism by which improvement occurs is unknown, but enough information is available to enable one to speculate on its possible mode of action. Cawadias[16] states that sulphur plays a very important part in the process of nutrition, particularly the nutrition of joints. Loeper and his associates[17] have noted that the neutral sulphur of the joint cartilage in rheumatoid arthritis was reduced about one-third below normal while the total sulphur of the blood was increased. They also noted that the amount of glutathione in the blood was below normal in a few cases. Cawadias[18] and Race[3] found an increase in the urinary output of unoxidized sulphur and the latter believed that there was a deficient oxidation of sulphur in these cases. Schlesinger[19] concurred in the opinion of Hopkins[20] that glutathione exists in all cells and that it plays a very important rôle in all processes of oxidation and reduction while others believed that it aids in detoxication. The theory of deficient oxidation of the tissues of the arthritic has long been advocated by Pemberton,[21] who stated that as a result of impaired circulation in the joints there is poor oxidation and nutrition. This also concurs with the "suboxidative state" mentioned by Llewellyn.[22]

Sullivan[23] suggested that inasmuch as glutathione aids in detoxication, its deficiency, as a result of improper metabolism, might allow uncontrolled action of the noxious agent in the arthritic. He be-

lieved that the administration of sulphur in these cases prevented the normal body sulphur complexes from being diverted into other channels. A low blood glutathione and a low cystin content of the finger nails, therefore, might indicate that there is a deficient oxidation of sulphur in these cases and, as it apparently plays a part in oxidation and in the nutrition of the joints, this may be the underlying factor in sulphur therapy.

The low cystin content in 67% of the cases studied compares closely with the 65% of Sullivan and Hess[7] and the 75% of Neligan[10]. When there was a subnormal cystin content, it was usually increased with sulphur therapy both when it was given by the intravenous and the intramuscular methods.

Except in a few cases, there was a reduction of the sedimentation rate and non-filament cell count with sulphur medication but there was only a slight reduction following placebo medication. The cases showing improvement with colloidal sulphur therapy are, as a rule, those in which vaccine therapy is of the least benefit. In young people with rheumatoid arthritis, for example, the cystin content is usually normal and sulphur is of little benefit, whereas in older people with rheumatoid arthritis and in patients with mixed arthritis and osteoarthritis, the cystin content is frequently low and sulphur therapy is often beneficial.

Those patients who showed improvement in the focal symptoms also showed marked improvement in constitutional symptoms, *i. e.*, less fatigue, an improved appetite and gain in weight. They were less depressed and assumed a more cheerful attitude toward the disease.

Although our results have not been as encouraging as those reported by some authors, we believe that sulphur is a valuable agent in the treatment of arthritis.

Conclusions. 1. Fairly large doses (10 to 30 mg. twice weekly) of colloidal sulphur, as a rule, are well tolerated.

2. With the larger doses, however, some patients developed symptoms of toxicity, such as fatigue, drowsiness, headache, increased pain, stiffness or swelling of joints but they usually disappeared in 5 days and were never severe enough to cause anxiety.

3. When the cystin content of the finger nails was below normal, it was usually increased with sulphur therapy.

4. The percentage and degree of clinical improvement was greater in those patients with a subnormal cystin content than in those with a normal content.

5. The percentage and degree of clinical improvement was greater with sulphur than with placebo therapy.

6. Sedimentation rates and non-filament cell counts were reduced in those cases showing clinical improvement.

7. There was no significant effect upon the red and white blood cell counts.

8. We believe that colloidal sulphur is a valuable agent in the treatment of certain types of arthritis.

We wish to express our thanks to Miss M. Jordan and Miss J. Weitzman for their assistance in this study.

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THE BACTERIAL FLORA ASSOCIATED WITH FOREIGN BODIES IN THE TRACHEA AND BRONCHI.*

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When a foreign body lodges in the air passage ways there is an inflammatory response on the part of the tissues more or less severe.

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Jackson[1] and McCrae[2] have studied this response clinically. According to them it depends upon the type of the foreign body, its length of sojourn in the tracheobronchial tree, the amount of occlusion occasioned by it, the age of the patient, and subsequent infection. Their studies do not include the bacteriologic findings in these cases. This paper deals with the bacteriologic data incident to a foreign body in the respiratory tract.

With the exception of my preliminary report[3] on the bacterial flora and tracheobronchial foreign bodies there is no systematic study on the subject. A few references to isolated cases have been listed in the American and German literatures.

The Material. The material for this study has been furnished by the Bronchoscopic Department of this hospital, the services of Dr. Chevalier Jackson and his successor Dr. Louis H. Clerf. There were 243 patients with tracheobronchial foreign bodies. Cultures of samples of mucopus obtained bronchoscopically from the site of the foreign body in the air passageways form the basis of this report.

The method of collection of the mucopus from the respiratory tract is important. Having introduced a laryngoscope, the surgeon passed a bronchoscope through its lumen thereby avoiding contamination of the latter with oral secretions. The mucopus was collected on small sterile gauze swabs or by means of an aspirator passed through the bronchoscope. The latter method is preferable; the former a necessity when the secretion is scanty. The foreign body itself has never been cultured since in its removal it is usually contaminated with the secretion of the buccal cavity.

I believe that the microbic content of pus so collected is more representative of the bacterial flora in the lesion than that of expectorated material. The evidence for that statement is based upon the following data. Pure cultures of bacteria have very occasionally been obtained from pus so collected. Secretions aspirated from individuals with a normal tracheobronchial tree, upon whom diagnostic bronchoscopies were performed, have contained few organisms; occasionally none were recovered. It can be demonstrated by growths obtained from pus repeatedly recovered from the same pulmonary abscess or bronchiectatic cavity that there is a variation in the bacterial population depending on the season of the year. Cultures seeded simultaneously from the tracheobronchial and oral secretions, equal amounts of each sample having been used, yielded organisms more or less similar in kind but quantitatively different. This is reasonable since the secretion from the lower respiratory tract contaminates the oral cavity when it is expectorated. Though contested by some, nevertheless there is abundant evidence to support the view that bacteria are constantly getting to the lower respiratory levels from above. How long they live and how well they thrive there, is another problem.

As an additional test, Dr. Clerf had a metal collar fitted on the pus collector. It was so constructed that it fitted the bronchoscope snugly and prevented the collector from coming in contact with the lateral walls of the bronchoscope. A sufficient number of mucopurulent specimens were collected from the trachea and bronchi with and without the collar to justify the conclusion that this source of contamination is negligible.

Technique. Smears were made and stained by Gram's (Burke's modification) method. Acid-fast and other stains were employed when indicated. Most of the specimens were also studied by dark-field examination to determine the presence or absence of spirochetes. Samples of pus were directly seeded on beef infusion agar plates containing about 5% of human blood

and in 1% dextrose bouillon, dextrose hormone broth since 1927. All media had a pH value between pH 7.5 and pH 7.8. The cultures were studied and transfers were made at the end of 48 or 72 hours. The plates were kept for a longer period before being discarded. The usual standard bacteriologic methods were used to classify and identify the organisms.

Essential differences and additions to the technique outlined above were employed as here indicated. A portion of a large number of specimens containing pneumococci was injected into mice and the pneumococcus typed. When there was any reason to suspect tuberculosis, guinea pigs were inoculated and the material seeded on Corper's or Loewenstein's mediums. A number of anaërobic cultures were made. I employed several methods; an anaërobic jar combining air exhaustion, nitrogen replacement and removal of the residual air with pyrogallic acid and sodium hydroxid, Zinsser's and Spray's anaërobic plate methods, Liborius' method plus an oil seal and Buchner's and Tarozzi's methods.

To have a basis of comparison for the bacterial findings a brief résumé of some of the clinical factors is necessary. Foremost is the foreign body itself. Jackson[1] and later McCrae[2] have directed attention to the differences in the local and general reaction of the patient with different kinds of foreign bodies. They observed in general, that foreign bodies consisting of animal and plant substance occasioned marked reactions and that certain ones, such as the peanut, were very prone to be associated with grave clinical features. With this in mind I have divided the foreign bodies as follows: 76 inert objects, pins, safety pins, needles, tacks, buttons, nails, screws, toys, dental fixtures and instruments, wire, beads, pencil caps, bullets, celluloid, pebbles, glass, bird shot, and a primer cap; a second group consisting of 8 bones and 22 teeth; and a third group consisting of 73 peanuts, and a final group chiefly vegetal substances consisting of 21 nuts and nutshells other than peanuts, 5 heads of timothy grass, 7 corn grains, 10 beans (navy, coffee and lima), 9 watermelon seeds and 15 miscellaneous, including peas, wood, pills, meat, apple, carrot, prune, potato and fruit seeds.

Age exerts a profound influence on the course of the disease. In this group the ages ranged from 8 months to 67 years. The youngest, a very ill child, aspirated the head of a blade of timothy grass. It was located in the right main bronchus and was removed after 7 days' sojourn. From the pus, *Strep. hemolyticus, S. aureus, B. influenzæ, Diplococcus pneumoniæ* and *Micrococcus catarrhalis* were isolated. The oldest patient had a dental fixture in his left bronchus for 3 weeks and a day. There was a profuse growth of *S. aureus* with a few colonies of *Diplococcus pneumoniæ* on the plates. The distribution of foreign bodies relative to age is significant. In the inert group there are 3 peaks, the first between the second and third years, the second between the fifth and sixth years, and the third in the second decade. The greatest number of peanuts and other vegetal foreign bodies are aspirated between the first and second years of life while the maximum for the aspiration of teeth and bones is reached in the fourth decade.

An analysis of the lengths of sojourn of the foreign bodies in the respiratory tracts indicate that the largest number, 44, were retained from 1 to 2 weeks; a second group of 20 for 3 days, and a third of 9 for 1 to 2 years. One, a nail in the bronchus of the right lower lobe of a woman aged 24, was in the bronchus for 18 years. The pus contained *Strep. hemolyticus, S. albus* and *Micrococcus catarrhalis* and the comment on my record is "She is not very ill."

In 144 cases of which I have a record, 18 of the foreign bodies were in the trachea, a part of one was located in both main bronchi, 72 in the right main or stem bronchus, 33 in the right lower bronchus, 5 in the left upper bronchus, 47 in the left main bronchus, 11 in the left lower bronchus, 5 in the right upper bronchus, 1 in the lung and 1 in the (right) middle lobe bronchus. The amount of obstruction is difficult to tabulate. In some instances the obstruction was complete while in other cases there was good drainage in spite of the presence of the foreign body. There were all grades and degrees of obstruction. The authors cited above have directed attention to the foreign body that frequently acts as a ball valve.

TABLE 1.—BACTERIA ISOLATED WITH VARIOUS TYPES OF FOREIGN BODY.

Bacteria.	Times isolated.	Foreign bodies and percentages of isolations in: 76 inorganic.	22 teeth 8 bones	73 peanuts.	67 vegetal.
Streptococcus hemolyticus	63	22	26	26	29
Streptococcus viridans	85	25	43	31.5	44.7
Streptococcus non-hemolyticus	29	14.4	10	8.2	13
Diplococcus pneumoniæ	94	32.8	46.6	43.8	32.8
Neisseria (N. catarrhalis, N. sicca, N. flava, N. subflava, N. crassa, N. mucosus)	153	55	56.6	73.9	59.5
Corynebacteria	54	21	13	26	22
Staphylococcus pyogenes aureus	54	38	26.6	23.2	16
Staphylococcus pyogenes albus	65	33	43	42	31
Mycobacterium tuberculosis	1	1	0	0	0
Bacillus mucosus capsulatus	18	9.2	0	5	10
Hemophilus influenzæ	34	5.2	33	16	11.9
Bacillus coli communis	2	1	0	0	1.4
Bacillus coli communior	2	1	0	0	1.4
Micrococcus tetragenus	11	6.5	6.6	2.6	2.9
Bacillus bronchisepticus	1	1	0	0	0
Bacillus subtilis	1	1	0	0	0
Proteus vulgaris	1	....	1.3	0	0
Vibrio (unidentified)	2	2.6	0	0	0
Monilia (Castellani)	6	2.6	0	1.3	4.4
Bacillus fusiformis	2	2.6	0	0	0
Spirochæta	2	2.6	0	0	0
Actinomycetes	2	0	0	2.6	0

Results. Table 1 is a summary of the number of times each bacterium was isolated and the percentage of times it was isolated in each group of foreign bodies. I have classified the Neisseria as a group; they can hardly be regarded as very potent pathogens. For the same reason the Corynebacteria are put in a group. Corynebacterium diphtheriæ was never isolated. A certain ill-defined group of organisms, thread-like in structure, branching or non-branching, and referred to under many names, I have grouped as Actinomycetes. By Monilia I mean certain yeast-like organisms classified by Castellani. Mycobacterium tuberculosis was recovered

once from the bronchus of a tailor, aged 67, who aspirated a tooth a month prior to the time of taking of the culture. He had had tuberculosis for many years. In addition to the tubercle bacillus, *S. aureus* and *Diplococcus pneumonia* were recovered. Table 2 is a comparison between the more important bacteria and age groups. There is a sufficient number of cases from the first to the eighth years and in the first decade to provide some idea of the frequency of organisms at these ages. For the other ages the number of cases is too few for conclusions to be drawn. Cultures have practically always contained more than one kind of organisms. Pure cultures from this source are the exception rather than the rule. Sometimes as many as 7 or 8 kinds of bacteria have been recovered. I have purposely not listed anaërobic bacteria because the total number of cultures so made is not sufficient for comparisons. One point is reasonably certain, however, many of the cultures did not develop a growth under anaërobic conditions. The anaërobic organisms most frequently recovered were streptococci. They can be put down as anaërobic and partially anaërobic organisms. At one time in this study a rather large series of pneumococci were typed; by far the greatest number of these were of Type 4.

TABLE 2.—RELATION OF BACTERIA ISOLATED TO AGE GROUPS.

	Years.															
Age of patient .	0–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–20	20–30	30–40	40–50	50–60	60–70
Number of patients . . .	4	31	41	23	17	17	15	8	7	10	14	10	11	5	4	4
	Occurrence in per cent age.															
Streptococcus hemolyticus	75	22	34	34	29	13.5	26.6	25	14	40	32	20	18	40	50	0
Streptococcus viridans		48	29	43	64	29	66.6	25	14	50	50	80	35	20	50	0
Streptococcus nonhemolyticus		19	12	17.8	5.9	17	6.6	37.5	14	20	5	20	9	0	0	0
Staphylococcus albus	75	60	39	41	29	29	33	37.5	14	20	38	40	11	20	0	0
Staphylococcus aureus		35	19	17.8	41	17	26	87.5	28.5	20	33.3	30	0	60	50	25
Pneumococcus		60.9	22	5.2	35	11.6	40	25	25.8	0	33.3	40	35	40	25	0
B. influenzæ		12	12	17.8	47	5.9	20	12.5	14	20	33.3	20	0	60	0	0
B. mucosus capsulatus		19	9	4	17	0	6.6	0	14	10	5	10	9	0	25	25

Comments. Comparing the microörganisms recovered with the foreign bodies it is apparent there is little difference in the frequency of occurrence of organisms in the different series of foreign bodies. The figures for hemolytic streptococci have percentages which approach each other numerically. In the group of peanuts there were 43% of pneumococci against 32.8% in the other vegetable foreign bodies, and 46.8% among the teeth and bones. Since peanuts and other vegetable substances are of a similar nature and

teeth and bones dissimilar, the close numerical ratio between unlike foreign bodies and its disproportion in like ones makes it evident that the foreign body of itself does not influence the character of the bacterial flora. Similar differences may be observed for the other organisms such as the staphylococci, *Strep. viridans* and *H. influenzæ*. In brief the organisms and the foreign body bear no direct relation to one another.

In the comparison between bacteria and age groups the situation is similar. In those instances in which the groups are large enough the same kind of disproportion between age groups and bacteria is apparent. The same sort of thing is so obvious with regard to length of sojourn of the foreign body in the respiratory tract and its location there, that I have not deemed it necessary to exhibit tables.

One might ask if this study of the flora in these cases demonstrate anything worth while. I believe it does. Since the bacteria recovered from the lesions are similar to the organisms of the mouth it is reasonable to suppose that some of them were aspirated with the foreign body or that they were present at the site of the lesion when the foreign body was aspirated. This is even more apparent when one considers the presence of *M. tuberculosis* in an instance in which there can be no argument, since the patient was known to have suffered from tuberculosis for many years. The occurrence of organisms, rather unusual for the respiratory tract, like *Prot. vulgaris* and *B. coli* is fairly good proof of contamination of the foreign body with these organisms. Most of the microörganisms recovered, are capable of setting up pyogenic infections. Since the pus usually contained several kinds of bacteria, it is not possible to be absolutely certain which is the exact exciting agent. Yet there are certain characteristics of growth about some of these organisms that seems significant. Chief among them is the quantitative difference of growth of the bacteria on a single blood plate. Very often it happens that upon such plates almost all of the bacterial colonies are of one kind. There are colonies of other bacteria present but they are few in comparison. This phenomenon is particularly striking with reference to *S. aureus*. From my observations of bacteria isolated from several thousand pulmonary lesions other than those resulting from foreign bodies I have observed how often *S. aureus* exhibits this property in this instance and how rarely one sees plates seeded from the pus of a pulmonary abscess, or a bronchiectatic cavity like them. The latter lesions, however, are far more common. When such an incident occurs it is fairly good presumptive evidence that the organism is the likely etiologic factor.

With regard to the degree of severity of the lesion, one is not often able to restrict its cause to one or the other type of organism present. All of the evidence seems to point to the conclusion that other things being equal one kind of bacterium is as capable as another of producing severe reactions. One of the most noteworthy

features in this respect is the frequent occurrence of the pneumococcus in these lesions. Yet Dr. Thomas McCrae, remarking that he had not observed pneumonia in any of these cases, suggested that there is food for thought on the pathogenesis of pneumonia in this connection.

While the importance of the bacteria is not to be minimized in the reaction occasioned by this accident, the type of foreign body and obstruction to drainage are the more important etiologic factors. The lesions have many things in common with obstructive lesions elsewhere in the body such as an obstructed sinus, gall bladder, or ureter. Sooner or later infection follows in their wake. In the tracheobronchial tree this usually occurs earlier than in some of the other localities of the body and it is often more apparent because of the extreme youth of the patient and the danger to life.

Summary. 1. Cultures seeded from pus bronchoscopically collected from the trachea and bronchi furnish more reliable data on the kind of microörganisms there, than those seeded from expectorated material.

2. The bacterial flora present in the air passages in which a foreign body is lodged does not materially change with the type of foreign body, its location or length of sojourn there, the age of the patient and degree of obstruction induced by it.

3. Other things being equal, one pathogen seems as capable as another of producing severe grades of infection in an obstructed tracheobronchial tree.

4. Quantitative differences in the numbers of colonies of different organisms on a plate of blood agar seeded from pus recovered from these lesions are a reliable guide in estimating the part that a given organism plays in the resulting infection.

5. The indications from a limited number of studies of the anaërobic bacteria from such lesions are that they are of minor importance.

6. The bacterial invasion and infection of the tissues of the lower respiratory tract at the site of a foreign body seem to follow the same general principles as those encountered in obstructive lesions elsewhere in the body. The irritation produced by the obstructing body itself and the amount of hindrance to drainage, primarily, and, secondarily, other factors favoring or hindering microbic multiplication such as the age and hardihood of the tissues, pressure on them and the duration of the irritation, determine and limit the infection.

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THE DIFFERENTIAL BLOOD PICTURE OF A GROUP OF RURAL INHABITANTS OF ALABAMA.*

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The functions of the eosinophils, the basophils and, to a lesser degree, the lymphocytes and monocytes, are not as well understood as are those of the neutrophils. Any observations which tend toward the explanation of their function or an analysis of factors associated with relative or absolute changes in the percentage of these elements in the blood should be of value. It is primarily for such a reason that this paper is written.

It analyzes the laboratory findings in 706 of the 849 persons studied during a public health survey in Bullock County, Ala., during 1934. In 143 no laboratory test or specimens were obtained for examination, for one reason or another. This survey was a house-to-house study to determine the prevalence of syphilis, positive tuberculin tests, malaria and intestinal parasites (chiefly hookworms) among the colored people living in and around Union Springs, Ala. Special care in the survey was given to environmental and related factors. When more cases are worked up, an attempt will be made to analyze the influence of these socio-economic factors. In this report, divided into five groups, however, we shall give only the laboratory findings.

There were 462 persons in the first group; 401 of them were between the age of 5 and 34 years. The differential white cell counts are given of these 401 persons who were our "normals" in that they did not have either a positive malarial smear, animal parasites in the stool examination, a positive tuberculin, or history of any of the diseases generally associated with an increase of eosinophils. In the second are the results of 47 persons with positive stool examination for intestinal parasites, chiefly hookworms or ascarids. In the third are the results of 71 persons whose blood smears showed malarial parasites. In the fourth are the results of 60 persons in whom the tuberculin tests were positive. In the fifth are the results of 153 persons who gave some history or showed some symptom that might be regarded as related to an existing increase in eosinophils. Among the conditions considered in this last group are asthma, hay fever, various types of skin lesions, history of food sensitivity or of previous serum inoculations.

* This study was made under the direction and advice of the Rockefeller Foundation.

GROUP I. "NORMALS." All of the persons of Group I were objectively and subjectively healthy. A complete white cell differential examination of one or more blood smears from each of them was done. Between 100 and 250 white blood cells were examined from each person. The percentage of the eosinophils and of the number of granules in these eosinophils appeared to be higher than that usually accepted as normal in most laboratory manuals. These results were arranged into seven classes according to age and are given in Table 1.

Because of the small number of infants or very young children examined and the highly labile erythrocytic and leukocytic blood picture in young children, as pointed out by Goldhamer,[1] in 1932, Klenerman[2] and others, in 1934, their results are not recorded in the table. The eosinophil and monocyte percentages were higher than for the class from 5 to 9 years.

TABLE 1.—THE AVERAGE PERCENTAGE DIFFERENTIAL OF WHITE BLOOD CELLS IN A GROUP OF APPARENTLY HEALTHY INDIVIDUALS LIVING IN ALABAMA.

Age group, yrs.	Neutrophils, %	Eosinophils, %	Basophils, %	Lymphocytes. Small, %	Lymphocytes. Large, %	Monocytes, %	Number examined.
5– 9	51.0	12.7	1.7	15.1	11.2	8.0	110
10–14	54.0	9.0	0.9	16.0	12.0	8.1	97
15–19	54.3	10.3	0.5	13.1	11.0	10.3	67
20–24	55.7	8.1	0.8	10.0	18.3	7.9	41
25–29	64.0	7.0	1.0	12.0	10.8	6.0	50
30–34	61.3	5.9	0.0	18.3	9.0	7.0	36

Even when our adults were compared with the differential graph of Needles[3] (1932), there are cellular differences, of which only the eosinophil differences are statistically significant. Needles'[3] results, obtained from 100 nurses, and our results from 158 individuals between the ages of 15 and 30 years, are as follows:

	Neutrophils, %	Lymphocytes, %	Monocytes, %	Eosinophils, %	Basophils, %
Needles' figures	70.0	24.6	3.2	1.7	0.5
Our figures	57.3	24.3	8.3	8.6	0.7

All of our smears were stained with either Wright's stain for blood films or Giemsa's blood stain. In our group the 24% lymphocytes were 11% small lymphocytes and 13% large lymphocytes.

The average number of granules in the eosinophils is given in Table 2. The total number of granules is counted in 2 eosinophils from at least one of the slides from each person recorded. These two eosinophils from each slide that were counted constitute as nearly a random sample of normal eosinophils as was possible. The objective of the microscope was focused on different parts of different slides, and the granules in the first 2 eosinophils that came into the field of the objective were counted. By varying this with each slide, we were able to avoid the effects of margination fre-

quently seen in the more sticky leukocytes in blood smears. Eosinophilic myelocytes were excluded from this table, so the results in Table 2 are of normal eosinophils with 2 or more lobes in their nuclei.

Realizing that many of these persons ate pork which was not government inspected and which might result in a mild trichinosis, special efforts were made to exclude such cases from this group by history. No biopsies were done.

TABLE 2.—THE AVERAGE NUMBER OF GRANULES IN EOSINOPHILS IN DIFFERENT AGE CLASSES.

Age group, yrs.	5 to 9.	10 to 14.	15 to 19.	20 to 24.	25 to 29.	30 to 35.
Eosinophil granules	140 ±6.2	109 ±6.6	110 ±6.6	114 ±5.2	94 ±5	101 ±6.4
Persons examined	16	11	10	10	17	6

Considering the reports of Biggart[4] (1932) and of Stephens[5] (1935) of the probable proliferation of some of the eosinophils from sources other than the bone marrow, palpation was done to determine the prevalence of superficial lymph adenopathy and enlarged spleens. There was found in this group a higher incidence of non-tender palpable lymph nodes, but the splenic index was less than in Group III, where the blood was positive for malaria and where the eosinophils were lower.

From the graphs of Custer and Ahlfeldt[6] (1932), a composite graph may be made which shows the variation in the cellularity of the bones of the tibia, femur, ribs, sternum and vertebra with changing age. When a composite graph showing the red (blood-forming) marrow is compared with the eosinophil changes with age, the correlation is very high up to the age of 15 years. We feel that some additional knowledge may be obtained by a more careful study of the cellularity of bones in animals in which a high eosinophilia may be produced, along with anaphylactic studies in animals. Any definite displacement of yellow (fatty) marrow by red (blood-forming) marrow, if carefully controlled and correlated with the changes in the cellular elements of the blood under acute experimental controlled conditions, would appear of value. We are outlining a protocol for such an experiment with the aid of the Department of Pathology.

The purpose of eosinophil increase is apparently defensive, acting not against bacterial diseases, but chiefly toward detoxifying, destroying and removing incomplete protein metabolic products which are injurious to the body. Hadwen[7] (1925) also thinks that the eosinophils may secrete substances which are injurious to the worms themselves in helminth infestation.

Since Klinkert[8] (1911), Armand-DeLille, Hurst and Sorapure[9] (1930), and Stewart[10] (1933), there have been reported cases of "familial" or "constitutional" eosinophilia in which persistent and unexplained eosinophilia of a high degree occurred in certain families. We attempted to analyze our cases to see if the high average percentage was peculiar to certain families. It did not appear sufficiently definite as a family trait to explain the high average eosinophilia.

With the demonstration of the clinical significance of the different nuclear forms of the neutrophils by Arneth[11] (1904), and the correlation of these changes with hematopoietic activity by Schilling[12] (1920), several investigators have recorded observations and discussed their significance (Cooke and Ponder[13] [1927], Farley and others[14] [1930], Kohlman[15] [1931], Mullin and Large[16] [1931], Fitz-Hugh[17] [1932], Gorsky[18] [1932], and Needles[3] [1932]). Most of their discussion centers around the diagnostic and prognostic value of a more efficient interpretation of the changes in the percentage of cells of the neutrophilic series when divided according to the age of the cell or their nuclear configurations. The importance of repeated counts on the same individual is emphasized, in order to determine not only the percentage at any one time, but the various types of shifts.

We present, for comparison with Needles[3] (1932) in normal nurses in Michigan, a hemogram of 100 similar count on 158 apparently healthy negro adults in rural Alabama between the ages of 15 and 29. In my group, the males and females are about equal.

Class.	I.	II.	III.	IV.	V.
Normal nurses (Needles)	8.4	22.9	26.7	8.7	3.2
Our normal negroes	11.0	17.6	18.9	7.6	1.9

The neutrophils were 57.3% of the white cell count in our series. In this hemogram, Class I represents the non-filaments, while Class V represents those of 5 nuclear lobules connected by filaments.

Group II. Persons Harboring Intestinal Parasites. Under the heading of monocytes are placed both the large mononuclears and the transitionals because they respond to the same stimuli, probably coming from the reticuloendothelial system, according to Gorsky[18] (1932). According to Poindexter[19] (1934), the platelet response is associated with the same stimuli. In 1 boy, aged 8 years, who was highly infested with hookworms, as determined by the Stoll count, there was found not only 31% of eosinophil leukocytes, but also 4% of eosinophilic myelocytes with their rounded, non-lobed nuclei. While we did not rule out a malignant tumor or leukemia, we could not find any further evidence to suggest either of them.

TABLE 3.—THE AVERAGE DIFFERENTIAL WHITE CELL COUNT ACCORDING TO AGE IN 47 PERSONS WITH INTESTINAL PARASITES.

Age group, yrs.	Neutrophils, %	Eosinophils, %	Basophils, %	Lymphocytes. Small, %	Lymphocytes. Large, %	Monocytes, %	Number examined.
5–14	48.1	21.7	0.6	12	9	9.0	26
15–24	53.0	14.9	0.9	12	12	6.1	14
25–35	62.6	12.5	0.6	11	9	3.1	7

GROUP III. PERSONS INFESTED WITH MALARIAL PARASITES. Table 4 gives the results of persons who gave a positive blood smear for malarial parasites. While some of these patients were very anemic and gave a history of chills and fever at various times within the last year, none of them was confined to bed or acutely ill at the time the blood smears were taken.

TABLE 4.—THE AVERAGE DIFFERENTIAL WHITE CELL COUNT ON A GROUP OF 71 INDIVIDUALS FROM WHOM A BLOOD SMEAR WAS POSITIVE FOR MALARIAL PARASITES.

Age group, yrs.	Neutrophils, %	Eosinophils, %	Basophils, %	Lymphocytes. Small, %	Lymphocytes. Large, %	Monocytes, %	Number examined.
5–14	53.9	6.4	1.0	13	15	10.0	37
15–24	57.0	6.0	1.3	12	12	10.6	22
25–35	62.1	4.9	1.3	13	11	6.8	12

The two chief observations here are the lower eosinophil and the higher monocyte percentage. The latter is what would be expected, but the former is still controversial. Some observers contend that there is an eosinophilia in chronic malaria, while others say that there is a decreased eosinophil percentage with the increase in anemia from the malaria. In this group, which is composed primarily of carriers, we did not find a high eosinophil percentage. The differential blood picture did not correlate highly with that of patients inoculated with the malarial parasite for the treatment of paresis, as reported by Winfield[20] (1932).

GROUP IV. PERSONS WITH POSITIVE TUBERCULIN TEST. Table 5 shows the results of a study of the differential count of a group of persons living in rural Alabama who reacted positively to an intracutaneous injection of 0.01 mg. of O.T.

TABLE 5.—AVERAGE DIFFERENTIAL WHITE CELL ON A GROUP OF 60 PERSONS WHO GAVE A POSITIVE TUBERCULIN REACTION.

Age group, yrs.	Neutrophils, %	Eosinophils, %	Basophils, %	Lymphocytes. Small, %	Lymphocytes. Large, %	Monocytes, %	Number examined.
5–14	56.1	8.5	0.8	16	14	4.5	19
15–24	61.0	5.9	0.8	15	12	4.1	30
25–35	62.1	3.8	1.1	15	13	4.1	11

Of the 706 individuals who had various tests and examinations, 576 had the tuberculin test. Sixty (10.4%) gave positive tuberculin.

When these results were divided according to age, 6% of those between the ages of 5 and 14 years gave positive tuberculin; 19% between 15 and 24 years and 21% between 25 and 35 years. The highest incidence was among those who gave a history of working or living in the nearby towns or city during the season when they were not planting or harvesting.

GROUP V. MISCELLANEOUS. The results of this group are listed in Table 6. This group contains a miscellaneous group of 153 individuals who either gave a history of some type of sensitivity or dermatitis. One case in this group was infested with Cochliomyia macellaria at the time the smear was taken. None of them was confined to bed at the time the blood for the differential was taken.

TABLE 6.—DIFFERENTIAL BLOOD COUNT IN CASES OF SENSITIVITY OR DERMATITIS.

Age group, yrs.	Neutrophils, %	Eosinophils, %	Basophils, %	Lymphocytes. Small, %	Lymphocytes. Large, %	Monocytes, %	Number examined.
5–14 . .	56.1	9.0	1.1	17	14	2.9	40
15–24 . .	59.6	11.4	1.0	13	11	3.8	64
25–35 . .	64.3	11.6	1.0	11	10	2.6	49

Discussion. While least is known about the function of the basophils, the eosinophils certainly appear to be next. The frequent association of hypereosinophilia with certain clinical conditions and following sensitivities of certain types of parenteral protein administration, has been sufficiently frequent to warrant the hypothesis that it is a response to incomplete protein metabolic products in the body.

Kelly[21] (1935) reports a 92% eosinophilia in a boy, aged 10 years, with 180,400 white blood cell count. The only positive facts were a pain in the joints, a history of fever and a questionable cardiac murmur and an enlarged spleen. He thinks that certain persons have a highly sensitive blood-forming system and an allergic response to a stimulus, which may express itself in the form of hypereosinophilia instead of by a temperature or skin reaction as seen in certain responses to bacterial or animal proteins or pollens.

A report of eosinophilia in a case of dermatoneuromyositis by Sluczewski[22] and others (1931), in which no other explanation was found, and the reference of Stitt[23] (1917) to the belief of Neisser that increased eosinophils may be due to an expression of the sympathetic system irritation, places that system under scrutiny. McCullogh and Dunlap[24] (1932), however, did not find the eosinophil percentage markedly disturbed in either hyperthyroidism or hypothyroidism. Cooke[25] (1932) thinks that the hereditary (atopic) factor in asthma, while not causal, may be responsible for the creation of an offspring of a more sensitive system, with a tendency toward the capacity for allergic manifestation, and the hematopoietic system, from which the eosinophils come, may be a part of this

inherited sensitive system to allergic or anaphylactic reactions. The system from which the eosinophils come may be either the bone-marrow, hemolymph nodes or their equivalents.

Animal experimental evidence and clinical observation have led Banerji[26] (1933) and Chillingworth[27] (1934), to believe that the increased eosinophilia in asthma is associated with the overdistention of the alveolar spaces. Associated with this alveolar distention are repeated forceful expiration, increase in carbon dioxid tension and probably disturbance of the acid-base equilibrium which may reflexly stimulate the sympathetics.

The explanation of the differences in percentage of some of the formed elements in the blood of this group of rural negroes living in Alabama, when compared with the average for the country as a whole, or with studies in a northern state, as Michigan, is not known. Whether there are racial, meteorologic, occupational, nutritional or obscure infectious factors which seem to be able to change the pattern of a differential count, are points which further study may clear up. The dietary habits of most of these people were conducive to vitamin deficiencies. While the cases of pellagra occasionally seen were not included in these averages, mild cases in the early stage may have been included unknowingly. This is especially worthy of thought when we realize that the dermatologic manifestations, which generally attract our attention, are secondary to neurologic damage. In this way the effects may be at work for a long time before they are externally manifested. The findings of this group compare favorably with those of a group of natives of Guam who were similarly studied. We hope others who may be interested in these facts may check them by similar studies of small localized groups under somewhat comparable conditions.

Because we did not find any parasites in the stools of the normals, we are not ready to say that the increased eosinophils were not associated with previous helminth infestations, since small numbers of ova in the stool, or a stool temporarily free from ova, are certainly not a criterion of previous infestation and not an absolute criterion of the absence of a small, relatively inactive female infestation, or a male infestation, either of which may cause some eosinophilia. This is probably not the case, however, as the age variation in the eosinophil percentage in the normal group did not correspond to the relative prevalence according to age, of hookworm infestation.

Summary and Conclusion. We have presented the results of our observations on white blood cell differentials from a group of rural negroes living in Bullock County, Ala. In laboratory studies, on 706 of the 849 persons studied, 401 were found to be free from animal parasites and other allergic diseases. These served as "normal" controls. This group, as well as the malarial positive, hookworm positive, tuberculin positive, and those with a positive listing of sensitivity, gave an average white blood cell differential

which does not correlate with that usually recorded in manuals as guides, and averages from more northern climates, and of persons of different occupations. The most consistent differences were a lower neutrophil percentage and a higher eosinophil and monocyte percentage in our group. This was true not only with those having some condition which could explain this difference, but also with the so-called normals. The most pronounced unexplained difference was the high eosinophil average. The average number of granules in the eosinophils was higher in those with the larger percentage of eosinophils. The question of whether these differences are racial, meteorologic, occuptional, nutritional, obscure, infectious, or a combination of these or other factors, is not answered.

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(Titles have been omitted for sake of brevity.)

BOOK REVIEWS AND NOTICES

DIET CONTROL. A System of Eleven Hundred Diets for the Prescription of Diabetic, Anti-obesity and Measured Diets in General. By GEORGE E. ANDERSON, M.D., Attending Physician to the Brooklyn and the Lutheran Hospitals; Chief of Metabolic Clinic, the Brooklyn Hospital, and PAUL CHADBOURNE ESCHWEILER, M.D., Assistant Attending Physician to the Brooklyn and the Methodist-Episcopal Hospitals; Senior Physician, Metabolic Clinic, the Methodist-Episcopal Hospital. Unpaged. New York: Gallo & Ackerman, Inc., 1935. Price, $3.50.

THIS unique offering presented in a loose leaf cover contains a blooklet of descriptive text relative to diet prescriptions. It offers a quick, moderately accurate presentation of caloric values and all necessary tables for establishing a dietary for the uncomplicated diabetic arteriosclerotic, diabetic children and the obese. Subsequent material consists in twenty individual diet booklets for the patient with readily understandable instructions and food table data.

The authors consider this a simple flexible method for the prescription of measured diets with ample latitude for modifications as the occasion arises.

The Reviewer feels that the material is aptly suited for workers in metabolic clinics and practitioners' offices where a ready dietary clearly presented is a necessity. The presented food tables lack in accuracy and completeness in relation to the rapid strides shown in the field of nutrition during the recent years, but they present the orthodox routine analyses.

M. B.

THE SPLEEN AND RESISTANCE. By DAVID PERLA, M.D., Associate Pathologist and Bacteriologist, Montefiore Hospital, and JESSIE MARMORSTON, M.D., Associate in Pathology, Cornell University Medical College. With a Foreword by DAVID MARINE, M.D. Pp. 170. Baltimore: The Williams & Wilkins Company, 1935. Price, $2.00.

THE effect of the spleen on resistance to infectious and metabolic diseases, neoplasms and other disorders has long been a subject that has engaged the attention of medical investigators, both for its scientific interest and practical importance in handling disease. This book presents not only a critical review of the complex literature on the subject but also the authors' not inconsiderable personal contributions. In the important question of the relation of the spleen to bacterial antibodies the authors conservatively conclude that it has a marked ability to fix antibody, and that its importance in antibody production is strongly suggested but not unequivocally established; it "is essential in the maintenance of the natural resistance" to certain infections in many species.

While the evidence is adequately presented and in general the deductions are acceptable, to some statements exceptions must be taken: the light area in the center of the Malpighian follicles definitely is not a "germinal center consisting of dividing lymphoblasts" (p. 6); neither should it be stated that "the spleen shows little or no change in any of the stages of acquired syphilis" (p. 38); objections to Evans' red and gray types of acute splenic tumor (p. 17) and reticulo-endothelial system (p. 46) are not well taken. Granted the need for resurvey of some fields in the light of

latent Bartonella and other infections, still it is very doubtful if the suggestion will stand that the spleen is of little importance in the metabolism of iron, though essential in the utilization of copper. In a field where there is so much difference of opinion and observation, the paucity of such objections is in itself a tribute to the value of this text, which is to be welcomed as a very useful contribution. E. K.

THE PROCEEDINGS OF THE CHARAKA CLUB. Vol. VIII. Post Multa Virtus Opere Laxare Solet. Pp. 202; illustrated. New York: Columbia University Press for the Charaka Club, 1935. Price, $5.00.

THE anticipatory pleasure of opening a new volume from this unique club of medical literati is heightened by the four-year wait that has followed the appearance of its seventh volume. Nor could any one be disappointed. The twenty-five articles are supplemented by a list of sixty-three contributions given but not published. Most important, perhaps, is S. W. Lambert's "Reading from Vesalius" on vivisection (Bk. VII, Chap. 19), which gives not only a translation and a photograph copy of the whole chapter in the second edition, but a trenchant essay on Vesalius' physiologic knowledge and on the ethics of vivisection. Sachs' eulogy of G. D. Stewart, a deceased member of the club, is followed by several delightful lyrics by Stewart scattered through the volume. The versatility of the members, though producing too many and varied articles to be considered here, well support their motto, "Post multa virtus opere laxare solet."
E. K.

THE DEPOPULATION OF PACIFIC RACES. Bernice P. Bishop Museum Special Publication 23. By S. M. LAMBERT. Pp. 42; 11 illustrations, 19 tables. Honolulu: Bishop Museum Press, 1934. Price, $1.00.

THIS study, conducted with the support of the Rockefeller Foundation, demonstrates that 1, in the Eastern Polynesian islands the native population has been reduced to a point that seems to preclude their racial regeneration; 2, the mixed native population of the mid-Pacific islands are safely on the upgrade, while, 3, the purely Melanesian islands of the west Pacific are still on the decline. The successful development of native practitioners in the Fiji and other mid-Pacific islands suggests that this may offer an important factor in the solution of the problem of racial regneration.
E. K.

NEW BOOKS.

Lilly Research Laboratories—Dedication. Pp. 128; illustrated. Indianapolis: Eli Lilly & Co., 1934.

Nutrition and Disease. The Interaction of Clinical and Experimental Work. By EDWARD MELLANBY, M.D., F.R.C.P., F.R.S., Late Professor of Pharmacology, University of Sheffield; Consulting Physician, Royal Infirmary, Sheffield; Secretary of Medical Research Council. Pp. 171; illustrated. London: Oliver & Boyd, 1934. Price, 8/6.

Diet and Physical Efficiency. The Influence of Frequency of Meals Upon Physical Efficiency and Industrial Productivity. By HOWARD W. HAGGARD, M.D., and LEON A. GREENBERG, PH.D., of the Department of Applied Physiology in Yale University. Pp. 180; 31 illustrations and 35 tables. New Haven: Yale University Press, 1935. Price, $3.00.

Lactobacillus Acidophilus and Its Therapeutic Application. By LEO F. RETTGER, PH.D., LL.D., Professor of Bacteriology in Yale University, MAURICE N. LEVY, M.D., Practising Physician, Bridgeport, Conn., LOUIS WEINSTEIN, PH.D., and JAMES E. WEISS, PH.D., Research Fellows in Yale University. Pp. 203. New Haven: Yale University Press, 1935. Price, $2.50.

The Surgical Clinics of North America, Vol. 15, No. 3 (Chicago Number—June, 1935). Pp. 239; 119 illustrations. Philadelphia: W. B. Saunders Company, 1935. Price, Paper, $12; Cloth, $16.

This Chicago number offers 9 articles in a Fracture symposium and 12 others on a variety of topics by well-known surgeons.

Die Werke des Hippokrates. Herausgegeben von DR. MED. RICHARD KAPFERER unter Mitwirkung von PROF. DR. GEORG STRICKER, Würzburg. Book 6 (Price, Rm. 7.50), Luft, Wasser und Ortslage (Air, Waters and Places); Book 9 (Price, Rm. 7), Die Diät (Lebensordnung) in akuten Krankheiten (Diet in Acute Diseases). Book 6, pp. 84; illustrated. Book 9, pp. 95. Stuttgart: Hippokrates-Verlag G.M.B.H., 1934. (To be published in 25 parts costing ca. Rm. 100, card binding.)

Child Psychiatry. By LEO KANNER, M.D., Associate Professor of Psychiatry, The Johns Hopkins University. With Prefaces by ADOLF MEYER, M.D., LL.D., Henry Phipps Professor of Psychiatry, The Johns Hopkins University, and EDWARD A. PARK, M.D., Professor of Pediatrics, The Johns Hopkins University. Pp. 527. Springfield, Ill.: Charles C Thomas, 1935. Price, $6.00.

Apparatus and Technique for Roentgenography of the Chest. By CHARLES WEYL, and S. REID WARREN, JR., Moore School of Electrical Engineering, University of Pennsylvania. Pp. 166; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, $5.00.

The International Medical Annual. Fifty-Third Year, 1935. A Year Book of Treatment and Practitioner's Index. Editors: H. LETHEBY TIDY, M.A., M.D. (OXON.), F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.SC., F.R.C.S., with 31 Contributors. Pp. 522; 60 illustrations and 64 plates. Baltimore: Wm. Wood & Co., 1935. Price, $6.00.

From "abdominal surgery" to "yellow fever" this useful annual made in Great Britian covers medical progress in 1934 in a very satisfactory manner.

The Medical Man and the Witch During the Renaissance. The Hideyo Noguchi Lectures. Third Series, Vol. 2 of the Publications of the Institute of the History of Medicine, The Johns Hopkins University. By GREGORY ZILBOORG, M.D., Pp. 215; illustrated. Baltimore: The Johns Hopkins Press, 1935. Price, $2.50.

Vier Vorlesungen über Kreislauffragen. Gehalten an der spanischen Universidad International de Verano en Santander. By DR. BRUNO KISCH, Ordentlichem Professor der Physiologie an der Universität Köln. Pp. 64; 6 illustrations. Köln: Paul Kuschbert, 1934. Price, Rm. 3.60.

NEW EDITIONS.

The Diseases of the Endocrine Glands. By HERMANN ZONDEK, M.D., (BERLIN), Director of the Medical Division, Bikur Cholim Hospital, Jerusalem, etc. Pp. 492; 168 illustrations. Third Edition Revised and Enlarged, Translated by CARL PRAUSNITZ, M.D., (BRESLAU), M.R.C.S. (ENG.), L.R.C.P. (LOND.), Honorary Research Fellow, Victoria University of Manchester, etc. Baltimore: William Wood & Co., 1935. Price, $11.00.

PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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ARTERIOSCLEROSIS AND RHEUMATISM

Arterial Calcification Associated With Renal Disease. Calcification of the arteries arises under certain circumstances. The variety usually encountered is the calcification of the media of the peripheral arteries which goes by the name of Moenckeberg's sclerosis. On the other hand, calcification also occurs in the areas of atheroma of the intima, and appears to be a deposition of the calcium salts in relation to the presence of fatty acids or their salts. Virchow long ago encountered a number of cases of metastatic calcification of arteries and other tissues arising as a process secondary to extensive destruction of the bony tissues. This type of arterial calcification is quite unusual. On the other hand, there is also a variety of calcification affecting the arteries, which is based on faulty metabolism. Such cases are occasionally encountered in very young children in whom no obvious lesion accounts for the widespread deposition of calcium in the arteries.

Hesse[1] describes the case of a woman aged 29 years, who in childhood had suffered measles, scarlet fever, renal incompetency and anemia, and in whom the renal condition became progressively more severe. She suffered occasional attacks of angina and on such occasions the urinary findings showed an acerbation of the kidney condition. At autopsy a generalized arteriosclerosis was encountered, the arteries being impregnated with a calcium deposit in the media. There was very little intimal change. This process of calcification affected the aorta and all of its branches even to the smaller visceral arterioles. The renal lesion was of the nature of glomerulonephritis with a great deal of contraction. The author, however, finding peculiar tubular changes, was inclined to believe that a congenital hypoplasia of the kidney had existed prior to the onset of the nephritis. In reviewing the description of these organs we cannot feel convinced in this latter interpretation.

It would appear that in this case the renal lesion was associated with an altered metabolism of calcium or a change in the secretory ability

of the kidney for calcium. There are no studies available to indicate whether this patient suffered from a hypercalcemia during life. The case, however, illustrates the development of calcareous deposits in the arteries under conditions of renal insufficiency.

Arteriosclerosis of the Arteries of the Tongue. In the many studies on the distribution of arteriosclerosis, evidence is available on the incidence of the condition in almost every artery of the body. Thiessenhusen,[2] however, points out that no contribution is available dealing with the presence of arteriosclerosis in the arteries of the tongue. He undertook an examination of a series of cases in which the lingual artery and its branches were dissected out and the character and distribution were noted. Some interesting facts arose in this investigation. The author points out that the muscles of the tongue are probably in greater activity through life than any other muscle group. The lingual arteries continue to develop and increase in thickness of the media up to 20 years; from then on until the fifth decade the arteries remain fairly constant in their size; after the fifth decade the media again begins to increase its diameter. The intima varies greatly in thickness, sometimes showing some diffuse thickening, at other times showing nodules. This intimal change is not accompanied with the deposition of fat and is not of the nature of atherosclerosis. It appears to resemble the hyperplastic overgrowth of the intima in which the elastic fibers increase in number. He noted that the internal elastic lamina from 5 years onward always showed more or less splitting. Furthermore, after the age of 29 there was a deposition of calcium in some portion of the elastic fiber; with age this deposition increased until the vessel was completely encircled by a calcareous ring. Not uncommonly an extensive calcification of the internal elastic lamina was unaccompanied by other changes in the intima. The author is unable to offer any explanation for this curious arterial change unless it is assumed that through the activity of the artery the elastic fibers suffer certain chemical and physical changes allowing the deposition of calcareous granules.

The Relation of Atherosclerosis of the Abdominal Aorta, the Carotids and the Carotid Sinus to Rheumatic Fever. The initiative for this pathologic study arose through the discussion by Weil at the recent Utrecht Conference, in which he indicated that a very large proportion of disease conditions in man had their origin in rheumatic infections. This again gave rise to the controversy, as to what shall be determined as rheumatic. Clinically it is very difficult to make a clear differentiation by symptoms alone, while the laboratory tests during life are still insecure. The pathologist, however, has the opportunity of utilizing a criterion, which is fairly satisfactory for determining the rheumatic condition, by the Aschoff nodule. In general the authors are agreed that this curious reaction arising in the various tissues of the body is distinctive for the rheumatic state. A difficulty, however, does present itself in accurately defining the Aschoff nodule. Gigante,[3] working under the direction of Aschoff at Freiburg, studied a series of arteries to determine a relationship between rheumatic disease and atherosclerosis. The investigation was particularly directed to an analysis of the abdominal aorta, the carotid arteries and the carotid sinus. The attack by rheumatism upon the ascending limb of the aorta with the development of nodular reactions, like Aschoff nodules in the adventitia

and the media, has been demonstrated by Klotz, Pappenheimer and others. It has always been claimed that the rheumatic lesion selects the ascending limb of the aorta and that its presence in the abdominal aorta was unusual. Subsequently Klinge claimed to have found the lesion not uncommonly in the abdominal aorta and associated with the development of atherosclerosis. Gigante studied 30 cases ranging in ages from 26 to 81 years, who died from a variety of conditions, some of whom had an antecedent history of rheumatic fever. He has failed to discover a single rheumatic nodule in the abdominal aorta, the carotid artery or the carotid sinus. He lays particular emphasis upon the negative findings in the vessels in a case in which the myocardium was thickly seeded with typical rheumatic nodules. Furthermore, he has failed to discover specific types of scarring which might have resulted from previous rheumatic involvement. Many of the arteries showed typical atherosclerosis of the intima and not uncommonly these intimal lesions were associated with a vascularization of the media immediately opposite to them. However, he notes that this vascularization appears in the vascular wall of rheumatic and non-rheumatic cases indifferently. The presence of advancing capillaries from the adventitia through the media towards the intima takes place whenever a severe nodular process arises in the intima, but the author could find no correlation of this response to the presence of a rheumatic condition in the individual. The author also comments upon the finding of non-specific reactions with lymphocytic infiltration following the course of the capillaries in the adventitia and media. These lymphocytic aggregations seem to have no relation to any particular condition in the individual. He indicates that their presence must not be confused with the true Aschoff nodule.

Acute Rheumatism. A group of British investigators undertook to evaluate the importance of some of the etiologic factors of rheumatism which have been advanced by others. In speaking of rheumatism they refer to acute rheumatic fever. Recent years have emphasized the importance of a group of streptococci in the precipitation of an attack of rheumatic fever. It soon became apparent that the streptococci, which were found in the upper respiratory tract in this disease, did not fall into a single cultural class, although they possessed immunologic similarity by which they were identified. Many have not been satisfied with the evidence incriminating the streptococcus as the causal agent of rheumatic fever, and have indicated in support of their contention the want of uniform findings during the acute phase of the rheumatic disease. Distinction must be made between the acute tonsillitis and the rheumatic attack which follows after an interval. It was this interval or "silent interval" which attracted the attention of the British workers. Schlesinger and Signy[4] pointed out that usually a silent period of from 10 to 21 days intervened between the rheumatic relapses and the tonsillitis or pharyngitis, which almost invariably preceded them. In a later communication[5] these authors have revised the length of the silent period to 2 to 4 weeks. It is during this silent period that certain events are taking place, some of which may be detected by serologic methods. During this period, these authors have found that there is a specific precipitin reaction demonstrable by the addition of the patient's serum to an antigen prepared from strains of

streptococci. All strains of streptococci do not serve for the production of this antigen. The nuclear protein of a hemolytic strain of streptococci isolated from the throat of a rheumatic case appears to give the best results. Nevertheless on continued cultivation of these streptococci the antigenic properties rapidly diminished. Other strains of hemolytic streptococci such as those isolated from strains of scarlet fever or from cases of non-rheumatic tonsillitis are not as valuable for antigen in the precipitin test. The authors also studied the value of the globulin and albumin fractions from these streptococci for their antigenic properties. In studying the series of rheumatic patients in respect to the precipitin reactions the authors made some interesting observations. The precipitin response appeared shortly after the development of the tonsillitis or pharyngitis and increased in intensity for a period of 3 or 4 weeks, although a number had their highest titer at a little later period. The reaction appeared to be directly related to the streptococcic infection of the throat and bore no relation to the intensity of the rheumatic manifestations which appear subsequently. It was noted that the height of the precipitin reaction determined the time of onset of the rheumatic attack; in other words it appeared that the immunologic response to the presence of the sore throat induced by a special variety of streptococcus was the warning of the onset of a new group of symptoms recognized as rheumatic fever. From this finding the authors suggest that the streptococcus plays a part in increasing the susceptibility of the individual to some other agent which initiates the rheumatic disease. The authors have studied many controls including cases of scarlet fever, non-rheumatic tonsillitis, subacute bacterial endocarditis and other streptococcal conditions. A certain number of these gave rise to a precipitin reaction not unlike that in rheumatic fever. The significance of this is yet to be determined. The authors have also utilized antigens of other bacteria in relation to the production of a precipitin by the serum of rheumatic cases. It is interesting that with antigens of some bacteria, especially staphylococci, a common precipitin response is present both in the normal controls and in the rheumatic cases. As the investigations by these authors have led them to believe that an important other factor attacks these individuals with specific immunologic reactions, they have then turned to a search for such an agent. Their attention was drawn to the possibility of a virus, having symbiotic relations to the streptococcus.

The virus nature of the infection in rheumatic fever has been referred to by a number of authors since Vecchi first claimed to have found positive results in animal inoculation with bacteria-free filtrates (1912). The proof of the presence of a virus has not been entirely satisfactory and it has been contended that the type of experimental animal used accounted for the failure. Animals do not develop rheumatic fever in their ordinary life, while the usual laboratory animals appear to be quite indifferent to a number of infectious agents affecting man. The British authors, Schlesinger, Signy, Amies and Barnard,[6] utilized pericardial fluids of rheumatic cases which, when subjected to high speed centrifugation gave rise to a small precipitate which was analyzed in several ways. The sterility of the fluids was determined by cultural methods. Microscopic examination using the dark field method and with a magnification of 1000 diameters showed the presence of numerous

particles which could not be analyzed directly under the eye. A staining technique along with Barnard's method of illumination showed the presence of many particles of uniform character besides other indifferent masses. Such particles were not present in control fluids. They believe these particles represent the elementary bodies of some virus. Furthermore, they have also found that these small bodies are agglutinated by the sera of patients suffering from acute rheumatic fever and who are resisting the further progress of the disease. The sera of rheumatic patients in the quiescent stage failed to show an agglutination. Negative results were also obtained with the sera of normal patients and with patients suffering from non-rheumatic infections. The authors recognize the importance of the streptococcal infection as a factor in the etiology of the disease. It is suggested that the lowered resistance produced by such infections enables the virus to enter the body, or, if the virus is already lying latent in the tissues, allows it to assume active characters. OSKAR KLOTZ, M.D.

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HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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BRUCELLOSIS

BRUCELLOSIS (the most recent name for undulant fever, Malta fever and Mediterranean fever) is one of our newer problems in clinical and preventive medicine so far as concerns much of the world. Until approximately 10 years ago the disease was looked upon as confined exclusively, or almost exclusively, to the Mediterranean basin. Then came the work of Evans and others, showing that the disease was much more prevalent than had been recognized and, indeed, might be expected to occur any time in any part of the world. About 2000 cases are

reported annually in the United States but doubtless many are missed. Early in the history of the disease the clinical course was recognized as being varied, and erroneous diagnoses were the rule rather than the exception. Perhaps the most frequent mistake lay in designating undulant fever as influenza, but Evans mentions the disease being mistaken for "typhoid, malaria, rheumatic fever, endocarditis, tuberculosis, bronchial pneumonia and bronchitis." Erroneous diagnoses were perhaps to be expected even in connection with the relatively acute cases. It is therefore not in the least surprising to find that such diagnoses have been even more common in connection with cases of long duration. Because of its low mortality rate, undulant fever is not considered a major public health problem, but the disease produces in many cases such prolonged, debilitating symptoms that it should warrant the serious consideration of health officers everywhere.

In this country the usual source of infection is lower animals (particularly cattle and hogs) infected with the organism of contagious abortion. Infection by contact with cases of the disease in man is practically unknown and the patient need not be regarded as a source of danger.

Hardy[2] notes particularly the exceptional risk to packing-house employees, who, while furnishing but 0.1% of the population of Iowa, supply 10% of the cases of undulant fever. Infected swine are a more serious source of danger than infected cattle.

There are at present three recognized types of infecting organisms of the *Brucella* group. These types are associated characteristically with goats, cattle and swine, respectively. Any one of the types may, however, infect any species of animal.

The bacteriologic history is interesting. First, Bruce identified an organism as the cause of undulant fever in man; then Bang established an organism as the cause of contagious abortion in domestic animals, but those working with the two organisms in human and veterinary fields, respectively, failed to note the great similarity—indeed, the practical identity—of the organism of undulant fever in the human and of contagious abortion of farm animals. The work of Evans established the fact that for practical purposes the organisms from the two sources may be regarded as identical, and led to the relating of many cases of the disease in man to disease of cattle and swine. The relation of the disease in goats to that of man had already been established.

In general, it may be said that the pathogenicity for man is markedly less in the *abortus* type (that derived from cattle) than in either the *suis* or *melitensis* types (derived from swine or goats). However, it is possible to get a strain conforming to almost any type from almost any host.

It has long been known that arthritis and orchitis are common complications and sequellæ of brucellosis. Recently, Hardy[2] reported what appeared to be hitherto unrecognized complications, namely: meningitis, osteomyelitis, spondylitis and pleurisy with effusion.

Evans[1] believes that many long-standing cases are overlooked. It has been estimated that perhaps not more than 20% of cases are diagnosed correctly even when circumstances suggest the true nature of the condition; in cases with less obvious history of contact the percentage of cases diagnosed correctly must be very small. Evans refers

particularly to the misleading nature of the term "undulant fever," and notes: "There is to be found in the literature little information about the disabling chronic form of the disease in which, during long periods of many months of illness, there may never be a significant rise in temperature." Evans believes that many cases of chronic brucellosis are diagnosed incorrectly as neurasthenia, and considers as probable manifestations of chronic brucellosis the symptoms often attributed to a neurologic condition—"exhaustion, insomnia, irritability, and complaints of aches and pains for which no objective sign can be found." She suggests that before a case is labeled "neurasthenia," brucellosis should be excluded.

The diagnosis in chronic cases is difficult. Cultivation of the causative organism from the blood stream, so valuable in the diagnosis of acute cases, rarely is accomplished in the chronic cases. The agglutination test may give misleading negative results. A positive reaction by this test is highly significant but occasionally healthy individuals give a positive reaction, presumably due to subclinical infection with Brucella organisms. The skin test has not been used sufficiently in general practice to determine its utility.

There is enough evidence to indicate that the physician is likely to overlook brucellosis unless he is alert to the possibility of its existence when confronted with symptoms suggesting a variety of clinical conditions, acute or chronic.

In general, there are two important modes of transmission[3] but the relative frequency of infection by these cannot be determined accurately at the present time. First, we have contact of man with infected animals or animal products; this mode of infection is particularly common among butchers, veterinary surgeons, sausage makers and agriculturalists. Second is to be considered the possibility of infection from milk of infected animals. Classically, the milk of the goat is the source of infection, but the goat is of minor importance as a cause of undulant fever in the United States, save in the restricted area in the southwestern part of the country where goats are used to some extent to provide milk for human use. Milk from infected cattle causes many cases—just how many remains to be determined. It is rather significant that the disease is practically unknown in communities where pasteurization of milk is strictly carried out. The disease is widely recognized as likely to be contracted by those who carry on experimental investigations in the laboratory, and some authors make a separate group for cases of this type.

It is obvious that in the final analysis the eradication of this disease becomes a problem for the veterinary scientists, since infected domestic animals always constitute the ultimate source from which the disease is derived.

Not only are definitely diseased animals sources of infection but, according to Carpenter and Boak,[4] apparently normal animals may also carry the infecting organism.

Measures for the eradication of the disease from herds of cattle center around the elimination of animals shown by the agglutination test to be infected. In a number of States compaigns of this sort are under way, but it is too early to predict the effect these efforts may have on the public health aspects of the problem. In the meantime, until

those working in the field of animal pathology establish the final solution of this problem, steps may be taken that will obviate the occurrence of many cases. When milk is the source of the infection the easiest and simplest procedure is the requirement of pasteurization or, if this proves impracticable, boiling of the milk will serve equally well. Cases originating from contact theoretically are preventable by scrupulous care in the handling of infected animals or animal products. The use of rubber gloves would seem to offer satisfactory means of protection, although it must be admitted that we are not acquainted with any practical experience to confirm this.

With respect to treatment but little is to be said. The majority of cases may be expected to recover spontaneously within a month to 3 months—a few drag out indefinitely. Chemotherapy has been tried extensively and generally has not given results that are encouraging. Certain advocates of vaccine therapy have reported astonishingly good results; nevertheless, in the hands of others vaccines have failed.

G. W. McCoy, M.D.

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